CONTROLLED CARDIOTOMY SUCTION DURING CARDIOPULMONARY BYPASS

Piet Willem Boonstra

CONTROLLED CARDIOTOMY SUCTION IN CARDIOPULMONARY BYPASS

Stellingen

1. In klinische hartoperaties waarbij een hartlongmachine wordt gebruikt met een membraan oxygenerator, kan de mate van thrombocyten-activatie verder worden verminderd door gebruik te maken van een bloedzuigsysteem waarbij het gelijktijdig meezuigen van lucht wordt voorkomen.

   (Dit proefschrift).

2. De functionele behandeling van een gesloten humerusschachtfractuur met behulp van een brace volgens Sarmiento is een goed alternatief voor andere niet-operatieve behandelingen. (P Peeters, KJ Bongers, PW Boonstra: (in druk) Ned T Geneesk 1986).

3. Het profylactisch geven van propranolol als beta-receptor blocker voorkomt de paradoxale hypertensie direct na de resectie van een coarctatio aortae bij kinderen en zou derhalve een routine onderdeel moeten worden van de perioperatieve zorg bij deze kinderen. (SS Gidding, AP Rachini, R Beekman et al.: N Engl J Med 1985 312: 1224-8).

4. Het verdient aanbeveling om aan de opleiding tot cardiopulmonaal chirurg, naast de twee 3-maandelijkse stages in de volwasssen- en kinder-cardiologie, ook een 3-maandelijkse stage in de thorax-anaesthesie toe te voegen.

5. De appendectomie wordt in het algemeen gezien als de eerste grote operatieve ingreep van de chirurgische assistent in opleiding. Het is echter een ernstige misvatting deze ingreep ook als de eenvoudigste te beschouwen.

6. De chirurgische behandeling van een ernstige stenose in de "left anterior descending coronary artery" dient bij voorkeur te geschieden door een "internal mammary artery graft". (FD Loop, BW Lytle, DM Cosgrove et al.: N Engl J Med 1986 314: 1-6).

7. Bij de behandeling van ernstige onderkoeling bij verdrinking en bijna-verdrinking dient het gebruik van de hart-long-machine te worden overwogen.

8. Het gebruik van het scanningssyteem aan de kassa van supermarkten biedt niet alleen de klant maar vooral de eigenaar van de supermarkt grote voordelen.

9. Wie zijn eigen huisarts is, heeft een dwaas als patiënt.

10. Gezien de grote druk van de overheid op bezuinigingen in de gezondheidszorg, wordt het hoog tijd dat die overheid zorg draagt voor de invoering van het in vele opzichten kostenbesparend systeem, waarbij organen van potentiële donoren zonder toestemming van hemzelf of familie kunnen worden verkregen, tenzij de potentiële donor of zijn familie hiertegen uitdrukkelijk bezwaar maakt.

11. Teneinde een onrechtmatige verdeling van startbewijzen door de Vereniging "De Friesche Elfsteden" onder haar leden te voorkomen, verdient het aanbeveling om vóór de tocht de verplichting tot legitimatie bij de wedstrijdrijders uit te breiden tot de toertochtrijders. De verplichting tot legitimatie tijdens de tocht kan een onrechtmatige verdeling van startbewijzen door de leden zelf voorkomen.

Stellingen behorende bij het proefschrift „Controlled cardiotomy suction during cardiopulmonary bypass" van Piet Willem Boonstra.

Rijksuniversiteit te Groningen

CONTROLLED CARDIOTOMY SUCTION DURING CARDIOPULMONARY BYPASS

PROEFSCHRIFT
ter verkrijging van het
doctoraat in de Geneeskunde
aan de Rijksuniversiteit te Groningen
op gezag van de rector Magnificus
Dr. E. Bleumink
in het openbaar te verdedigen
op woensdag 23 april 1986
des namiddags te 4.00 uur.
door

Piet Willem Boonstra

geboren te Britsum

1986
DRUKKERIJ VAN DENDEREN B.V.
GRONINGEN

Promotores : Prof. Dr. Ch.R.H. Wildevuur
Prof. Dr. J.N. Homan van der Heide
Prof. Dr. G.F. Karliczek

Referent : Dr. F.E.E. Vermeulen.

Promotiecommissie: Prof. Dr. J.C. Dorlas
Prof. Dr. A. Eijgelaar
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CHAPTER 1
GENERAL INTRODUCTION

GENERAL INTRODUCTION

From the very first introduction of the extracorporeal circuit in open-heart surgery by Gibbon in 1937 (1,2), it has been recognized that blood cell damage in general and platelet damage in particular are important consequences of cardiopulmonary bypass (CPB)(3-5). Since the introduction of the extracorporeal circuit many components have been improved (6-8), but in rather less than 4 % of cardiopulmonary bypass operations severe postoperative bleeding of non-surgical origin still occurs (9-11).
Many studies have tried to elucidate the mechanisms of this non-surgical bleeding after CPB but the exact mechanisms are still not completely understood. Most reports conclude that the abnormal bleeding tendency after CPB is mainly caused by a poor platelet plug formation (9-19). This seems to be due to an impaired platelet function as well as to a decreased platelet number, caused by the contact of the platelets with the synthetic surface of the extracorporeal circuit and with the cardiotomy suction system (20-23). These contacts induce the formation of platelet aggregates and the release of platelet granular contents, but also a disruption of subcellular architecture of the platelets (14). Prior to the discussion of the contribution to platelet damage by the suction of blood during cardiopulmonary bypass, it is appropriate to summarize briefly current concepts of the platelet and its function in hemostasis.
Platelets are a-nuclear fragments of the giant bone-marrow cells, called megakaryocytes. Two platelet "storage pools" are known in man: the splenic pool and the non-splenic pool of unknown origin (24). Possible anatomic sites for the non-splenic pool are other reticulo-endothelial organs, in particular the lung, and margination to the endothelial vascular surface. Platelets are 1.5 - 2.0 μm in diameter and circulate in the blood in a concentration of 150-350x10^9/L. Their mean life span is about 10 days. Because platelets have no nucleus they have only very little ability to synthesize proteins, but they have an active metabolism concentrated in the mitochondria (25).
By electronmicroscopy the platelet looks like a sponge: one sees small elevations, resembling protuberances of internal organs, and small openings, resembling apertures thought to be openings of an internal funnel-shaped membrane system, called the surface-connected-channel-system (26). The external surface of the platelet consists of a glycocalyx, beneath which is a phospho-lipid bilayer, containing proteins (25-27). Inside the platelet are at least three types of granules: dense, alpha and lysosomal granules (27,28).

The contents of these granules are secreted when the platelet is stimulated. Dense granules are storage organelles for non-protenaceous substances, including calcium, pyrophosphate, serotonin and adenine nucleotides. The alpha granules are more numerous than the dense ones, and contain a variety of proteins, including beta-thromboglobin, platelet factor 4, fibrinogen and low-affinity platelet factor 4 (LA-PF_4), a protein which is mitogenic for smooth muscle cells, and coagulation proteins. The lysosomal granules contain a variety of acid hydrolases and proteases (15,27,29-32). Apart from these granules the platelet contains contractile actomyosin which, together with a circumferential band of microtubles inside the platelet, is responsible for the discoid shape of the unstimulated platelet (25).

When blood vessels are injured so that they bleed, circulating platelets adhere to the damaged vessel wall, in particular to subendothelial structures such as collagen, whereafter they aggregate (33). In particular factor VIII (Von Willebrand) plays an important role in this interaction between platelets and the vessel wall (34,35). But also coagulation factors, that are absorbed to the external surface of the platelet, play a part in the formation of the platelet plug (36,37). Substances in the vessel wall, in the plasma and both on and in the platelets themselves, thus act together to form the solid plug that arrests bleeding.

Platelets can be activated in vitro by interactions of chemical activators with receptors at the external surface of the platelet (37-42). But also physical activators, such as shear or osmotic stresses, can cause platelet activation in vitro, mediated by intracellular and membrane changes not yet identified. In particular high shear stresses can cause ADP and endoperoxide release from platelets and also from red cells (43-50). However, these high shear stresses can also directly disrupt subcellular structures of the platelets (45-48).

When heparinized blood is exposed to a synthetic surface such as that of an extracorporeal circuit in CPB, blood proteins are absorbed at the surface within seconds (14,49-52): fibrinogen in very high amounts, but albumin and globulin in smaller amounts (53). The amount of absorbed proteins appears to vary with the composition of the surface material (54). The protein layer formed in this way is an appropriate milieu for platelet adhesion (55). After adhesion, platelets undergo shape change, become sticky to each other and degranulate. Passing platelets adhere to them and also aggregate and degranulate (56). Subsequently within a few minutes after the start of extracorporeal circulation, the platelet number decreases to approximately 20% of the normal value and increases slowly thereafter (20,22,49). In vivo studies show that sequestration of platelets in the liver and the spleen also account for part of this decrease in platelet number (57).

In experiments on dogs, De Jong (22) nicely demonstrated the contribution to platelet damage of the various components of the extracorporeal circuit. He pointed out that the type of the oxygenator plays an important role in

the observed platelet alterations. Currently two types are used: first, the bubble oxygenator (BO), in which the gas exchange is accomplished by blowing oxygen through the blood and second, the membrane oxygenator (MO), in which the gas exchange takes place through a membrane. This latter system causes less trauma to blood proteins and lipoproteins, and causes less hemolysis and less damage to the platelets (21). However, this better hemocompatibility of the MO could not always be substantiated in cardiopulmonary bypasses in the more complex and less standardized clinical CPB (21,58-64). One of the reasons for this was the damaging effect of cardiotomy suction. In 1962 this source of blood cell damage was identified by Osborne (65). Others found that these effects were due to the shape of the sucker tip, to the height of vacuum suction and in particular to simultaneous aspiration of air (20,22,64-66). In addition, Wright (45) and Goldsmith (46) demonstrated in vitro that during air aspiration along with suction of blood, shear stresses are generated, which are able to cause a release of platelet granule contents or even a disruption of the platelet. So in order to reduce the shear stresses in vivo, the shape of the sucker tip was improved and the height of the vacuum suction was lowered. However, it took a very long time before one was able to prevent the aspiration of air along with suction of blood. In 1975 Arts and co-workers (67) developed an electronically controlled suction system, consisting of a special pericardiotomy sucker and a suction device, by which the aspiration of air along with suction of blood could be prevented. By using this controlled suction system, Ten Duis (20) and De Jong (22) demonstrated that platelet number and function and postoperative hemostasis indeed could be maintained at the level of an MO perfusion without any suction. However, these effects were only demonstrated in CPB on dogs.

In this thesis we will investigate the effects of cardiotomy suction during clinical CPB. We will evaluate the contribution of cardiotomy suction on platelet damage and postoperative hemostasis in relation to the type of operation as well as the type of oxygenator and the arterial line filter. Furthermore we will determine if platelet number and function and postoperative hemostasis can be improved, when during an MO perfusion controlled cardiotomy suction is used in conjunction.

One of the problems related with clinical studies is the large variation in the patient population, in particular in relation to the type of operation and its total volume of cardiotomy suction during CPB. In Chapter 2 this problem is evaluated, in order to identify a group of patients in which the variations of the amount of cardiotomy suction are acceptable.

In Chapter 3 we determine in standardized patient populations whether uncontrolled cardiotomy suction can indeed impair the platelet preserving capacity of the MO compared to that of the BO.

Because an arterial line filter is used routinely in BO systems, but not in MO

systems, the contribution of the arterial line filter to platelet damage was investigated separately in Chapter 4.
In Chapter 5 we introduce the controlled cardiotomy suction system clinically, in order to determine whether the prevention of air aspiration can indeed reduce platelet damage and can improve postoperative hemostasis and consequently can maintain the platelet preserving capacity of the MO.
Because the effects of the use of controlled cardiotomy suction on platelets during a BO perfusion are unknown, we evaluated platelet damage and postoperative hemostasis in clinical BO perfusions. (Chapter 6).
In Chapter 7 the conclusions of the previous chapters are summarized.

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CHAPTER 2

BLOOD RETURN DURING CARDIOPULMONARY BYPASS RELATED TO THE TYPE OF OPERATION AND PERFUSION TIME

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ABSTRACT

We measured total volume of blood return in coronary artery bypass grafting (CABG) operations (n = 100), and in valve replacement operations (n = 45). Total volume of blood return varied widely between 11.6 and 108.0 L. and expressed as a percentage of total blood perfused through the extracorporeal circuit it varied between 2.8 and 13.6 %. Matching the CABG and valve replacement operations for equal perfusion times of 1-2 hours, largest volumes were measured during the mitral valve replacement operations (46.3 ± 21.4 L)*, smaller volumes during the CABG operations (37.8 ± 14.9 L)* and smallest volumes during the aortic valve replacement operations (29.1 ± 18.1 L)* (not significantly different). Total volume of blood return was positively related with perfusion time only in the CABG operations and largest mean volumes were measured during perfusions of 3-4 hours (61.3 ± 24.9 L)*. So total volume of blood return varied widely between the different types of operation. Only in CABG operations did it correlate positively with the duration of perfusion.

*Mean ± standard deviation.

INTRODUCTION

Platelet damage during cardiopulmonary bypass can be reduced substantially by using a membrane oxygenator, whose hemocompatibility is superior compared to that of the bubble oxygenator (1-10). However, this reduction in platelet damage is considered to be lost by the damaging effects of cardiotomy suction (11-14). The cardiotomy suction system returns blood from the operation area back into the oxygenator system, but it is accompanied by the simultaneous aspiration of air. It introduces an intensive blood/air contact and shear stresses at the sucker tip and in the suction lines, known as a major damaging factor for blood elements (13,15,16).

The purpose of this study was to find a well defined group of patients in which the hematological effects of cardiotomy suction could be studied. Therefore total volume of cardiotomy suction, operation type and perfusion time had to be standardized (9,10,17). To evaluate this we measured total volume of blood return to the oxygenator in adults, which were subjected to cardiopulmonary bypass for coronary artery bypass grafting or for various valve replacement operations. We determined its relation with perfusion time as well as with the type of operation.

PATIENTS AND METHODS

Data from 145 patients requiring cardiopulmonary bypass provided the basis

for this study. The types of operation included 100 coronary artery bypass grafting (CABG) operations, 27 single valve replacement operations (21 aortic valve, 6 mitral valve) and 18 double valve replacement operations (aortic and mitral valve).

Total volume of blood return was defined as the total blood return from the operation area to the cardiotomy reservoir during cardiopulmonary bypass, via a cardiotomy suction line (¼ inch ID, PVC tubing), via a left ventricular decompression line (Sarns 10610, 18 Fr.; Sarns Inc., Ann Arbor, Michigan, USA) and via an aortic root venting line (DLP, 7 Fr.; Watson S.W., Grand Rapids, Michigan, USA) all with non-occlusive roller-pumps. These three suction lines emptied into a cardiotomy reservoir (Dideco D 641, Dideco s.p.a., Mirandola, Italy), from which the blood flowed by gravity to the venous reservoir of the membrane oxygenator (SciMed spiral coil, SciMed Life Systemes Inc., Minneapolis, Minnesota, USA). Besides the blood, also the solutions for cardioplegia and for continuous external cooling of the heart were aspirated via the left ventricular venting line as well as via the cardiotomy sucker. The total volume of these solutions did not exceed 5 L. The total volume of blood return was determined by integrating the blood flow signal, measured by means of an electromagnetic blood flow probe (Nycotron model 376/393, Nycotron, Drammen, Norway) in the blood outlet of the cardiotomy reservoir. Calibration of this unit was performed every 30 minutes during bypass. The perfusion time was defined as the summation of partial and total bypass time. Perfusion techniques and details of components of the extracorporeal circuit are reported elsewhere (18). For statistical analysis of differences between the groups, the Student's T test was used with a 5 % level of significance.

RESULTS

The total volume of blood return varied widely among the patients in all four types of operation ranging from 11.6 to 108.0 L.; expressed as a percentage of total blood perfused through the oxygenator, this percentage also varied widely and ranged from 2.8 to 13.6 %.

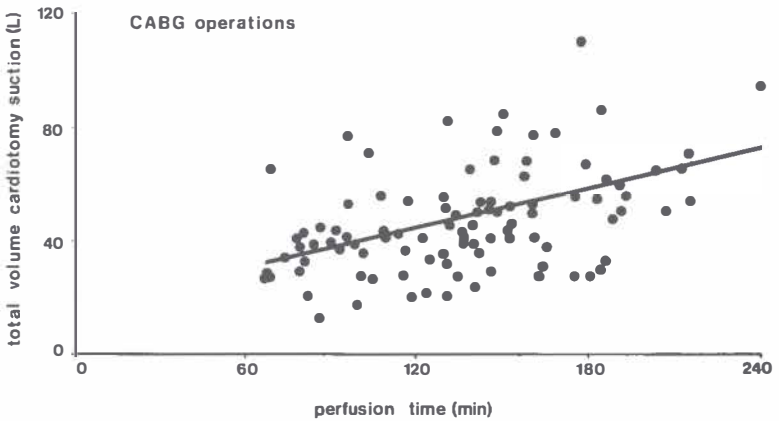
Only in the CABG operations the total volume of blood return correlated positively with the perfusion time: $y(L) = 16.9 + 0.2x(min)$, $r=0.46$, $p < 0.05$ (Fig.1 and Table 1).

Within the valve replacement operations, the largest mean volume of blood return was found in the mitral valve operations, a smaller volume in the double valve operations, and the smallest volume in the aortic valve operations (Table 1). However, differences between the groups were not significant.

In order to compare the volumes of blood return in the various types of operation, we selected those operations with perfusion times between 1 and

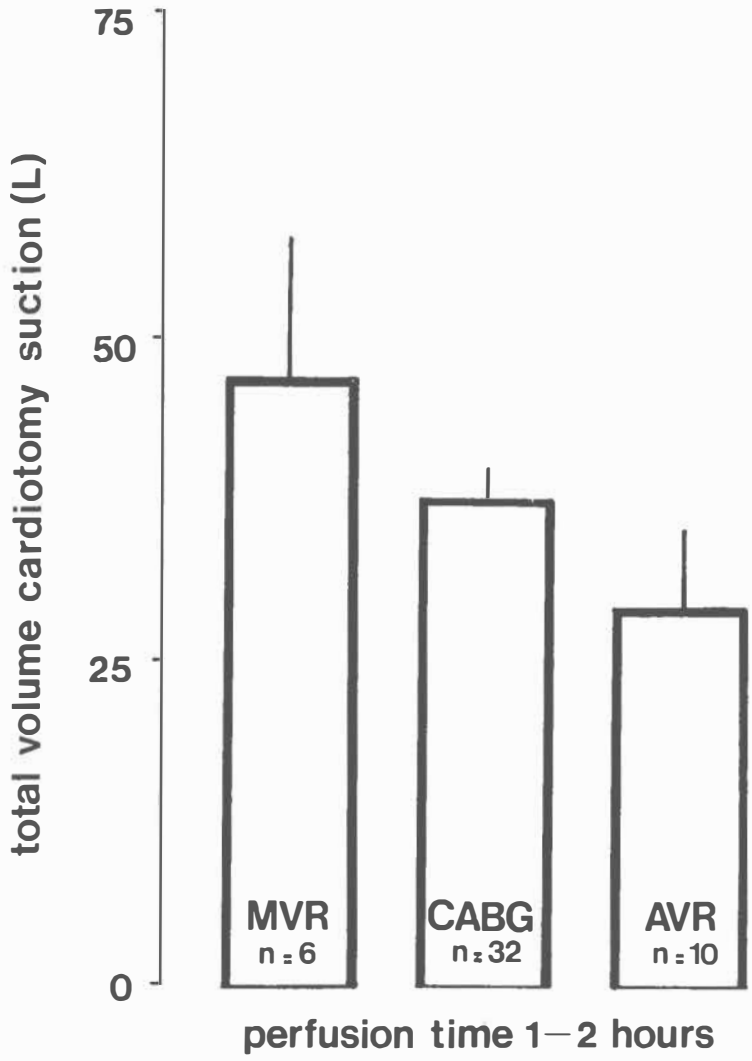
Table 1: Results of blood return measurements. All data are means ± standard deviation. CABG = coronary artery bypass grafting operation, MVR = mitral valve replacement, AVR = aortic valve replacement, DVR = double valve replacement operation.

operation	n	perfusion time (min)	blood return (L)	blood return as percentage of perfusate (%)
CABG (1-2 hours)	32	91 ± 16.0	37.8 ± 14.9	9.7
CABG (2-3 hours)	49	145 ± 15.3	50.0 ± 23.3	7.3
CABG (3-4 hours)	19	205 ± 22.4	61.3 ± 24.9	6.1
MVR	6	129 ± 20.0	50.2 ± 28.5	8.6
MVR (1-2 hours)	4	103 ± 10.9	40.2 ± 24.3	8.7
AVR	21	122 ± 21.1	32.5 ± 14.3	5.9
AVR (1-2 hours)	10	103 ± 8.0	29.1 ± 18.1	6.3
DVR	18	154 ± 18.0	38.5 ± 20.7	5.5



Legend to figure 1:
Relationship between total volume of cardiotomy suction and perfusion time in CABG operations (n = 100). Regression equation: y(L) = 16.9 + 0.2x(min)
r = 0.46, $p < 0.05$

2 hours. Then largest mean volume of blood return was found in the mitral valve operations followed by the CABG operations, whereas the smallest volume was found in the aortic valve operations (Fig.2). In the double valve operations nearly all perfusion times exceeded the time limit of 2 hours. Differences between the three groups were not significant.



Legend to figure 2:
Comparison of total volume of cardiotomy suction in 3 different types of operation, with an equal perfusion time of 1-2 hours (mean ± SD). MVR = mitral valve replacement, AVR = aortic valve replacement, CABG = coronary artery bypass grafting operation.

When the total volume of blood return is expressed as a percentage of the total blood perfused through the oxygenator, the percentage was highest in the CABG operations (9.7 %), followed by the mitral valve operations (9.3 %), whereas the percentage was lowest in the aortic valve operations (6.3 %) (Table 1).

DISCUSSION

We found that the total volume of blood return varied widely within as well as between the various types of operation, as was indicated by the wide variations in the means and standard deviation of total blood return of all types of operation. It has to be realized that the solutions for cardioplegia and for external cooling of the heart, somewhat obscured the total volume of cardiotomy blood return. However, this volume of maximal 5 L is relatively small compared to the total volume of blood return from the operation area.
Most probably due to the wide variations in the total volumes of blood return, we found no significant differences between the groups. In particular in the valve replacement operations, variations in the standard deviation were large, except those of the aortic valve operations. In contrast to the valve replacement operations, standard deviations were relatively small in the CABG operations. Furthermore only in the CABG operations total blood return was positively and significantly correlated with perfusion time. During short perfusions (1-2 hours), small mean volumes and during long perfusions (3-4 hours) large mean volumes of blood return were found. In order to compare the different volumes of blood return between the groups we matched each for equal perfusion times of 1-2 hours, but differences between the total volumes of blood return of the CABG and valve replacement operations were not significant. Again the standard deviation was smallest in the CABG operations compared to the other groups (Table 1).
Because of these facts we selected the CABG operations in which the effect of cardiotomy suction on platelet damage could be studied. In addition, in these operations mean total volume of cardiotomy return was large, so a maximal effect of cardiotomy suction on platelets can be expected in particular in the perfusions lasting 3-4 hours. Furthermore the patients of this group are a rather consistent population in regard to their age (19) and their acquired heart disease that is treated by a more or less standardized technique of CABG all over the world. These characteristics are in contrast to those of patients undergoing a valve replacement operation (19). Total volume of blood return is smaller and standard deviations are larger, their ages vary widely, the etiology of their disease is different and their operations implicate the implantation of different foreign material.
In this present study we did not involve patients with congenital heart diseases,

because this particular group of patients is less well defined, due to the fact that these patients are often little children with a very wide variation in the type of their congenital heart disease (19). Furthermore in these patients total volume of blood return varies widely as was demonstrated by Edmunds et al. (17) who studied 76 patients with congenital heart diseases.
So in order to study the hematological effects of cardiotomy suction, the CABG operations with an expected perfusion time of approximately 3 hours would be most appropiate since in this group of patients a large amount of blood return can be expected. Other types of operation or other perfusion periods are not warranted because of larger variations in the total amounts of blood return, larger variation in age and lower incidence when compared to CABG operations.

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CHAPTER 3

HEMATOLOGICAL ADVANTAGE OF A MEMBRANE OXYGENATOR OVER A BUBBLE OXYGENATOR IN LONG PERFUSIONS

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ABSTRACT

In order to determine whether large volumes of cardiotomy suction, which occur during long perfusions, can obscure the hematological advantage of the membrane oxygenator (MO) over the bubble oxygenator (BO), we studied 23 patients undergoing a coronary artery bypass grafting (CABG) operation with an expected perfusion time of 3 hours. MO group, n = 10, SciMed spiral coil; BO group, n = 13, Shiley 100-A.
During the MO perfusion we found significantly higher platelet numbers, better platelet function (ADP induced platelet aggregation) and less hemolysis (plasma hemoglobin), than during the BO perfusion. After the MO perfusion we measured significantly shorter bleeding times and less transfusions of blood products. However, blood loss and whole blood transfusions up to 18 hours after perfusion, did not differ significantly between both groups.
So in CABG operations with long perfusion times of approximately 3 hours, the MO still causes significantly less platelet and erythrocyte damage than the BO, despite the large volumes of cardiotomy suction known to occur during these operations.

INTRODUCTION

Platelet damage during cardiopulmonary bypass can be reduced if a membrane oxygenator (MO) is used instead of a bubble oxygenator (BO) (1-7). However, it has been indicated that this advantage of the MO can be obscured by the platelet damaging effect of cardiotomy suction (8-10), caused by the intensive blood-air contact, which induces turbulences and high shear stresses at the sucker tip and in the suction lines. The extent of this platelet damage is dependent on the total volume of cardiotomy suction (11,12), so consequently the platelet damaging effect of cardiotomy suction will be more apparent in those operations which require large volumes of cardiotomy suction, like during CABG operations with long perfusion times.
In order to determine whether these large volumes of cardiotomy suction indeed can obscure the hematological advantage of the MO over the BO, we studied platelet and erythrocyte damage and postoperative hemostasis during and after perfusions which lasted approximately 3 hours, using an MO or a BO and the conventional method of cardiotomy suction, implying the aspiration of air together with suction of blood.

PATIENTS AND METHODS

Ten patients were perfused with a membrane oxygenator (MO) system, SciMed spiral coil MO model 3500-2A (SciMed Life Systems Inc., Minneapolis,

Minnesota, USA). Thirteen patients were perfused with a bubble oxygenator (BO) system, Shiley 100-A (Shiley Inc., Irvine, California, USA) and an arterial line filter (Bentley Polyfilter, Blood bypass filter PF 427, Bentley Lab., Irvine, California, USA). Both systems were clear primed. Cardioplegia as described by Bleese (13) was used.

Platelet function was expressed by platelet aggregation, induced by adenosine diphosphate (ADP) in platelet rich plasma (PRP). Platelet number in each sample was adjusted to 75.000-100.000/ml. Platelet aggregation was assessed by measurement of the OD_{max}, which is the maximal procentual change in optical density of PRP after ADP induced platelet aggregation. Only in the pre-perfusion sample various doses of ADP were tested to induce platelet aggregation in order to find that ADP concentration, which resulted in a $\pm$ 65% change of the maximal achievable decrease in optical density ("second wave") of PRP. This ADP concentration was used in all following samples (14). Plasma hemoglobin was determined by a method as described by Drabkin (15). Pre- and postoperative bleeding times were determined in the volar skin of the fore-arm (Simplate II, General Diagnostics, New Jersey, USA) (16,17). Postoperative blood loss and transfusions of whole blood and blood products, were measured up to 18 hours after the end of perfusion. Whole blood and blood products were expressed in the number of donors necessary for the transfusion.

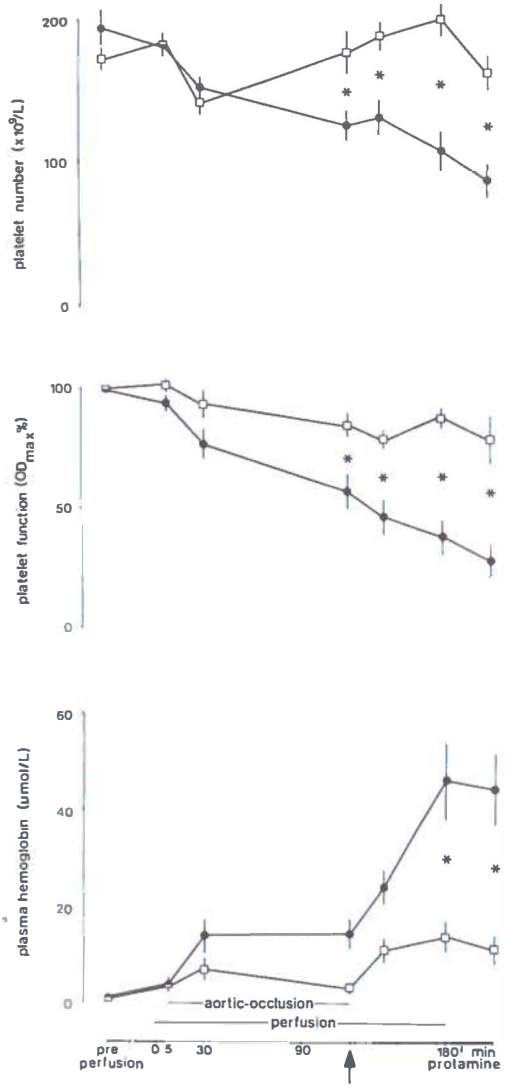
The Student's T test or the Wilcoxon's test were used for statistical analysis of differences between the two groups. Values of $p < 0.05$ were considered to be significant.

RESULTS

There were no significant differences between the patients of both groups in age, perfusion time, aortic crossclamping time, number of proximal and distal anastomoses and hypothermia temperature (Table 1).

In the BO group platelet number (corrected for hemodilution) and ADP induced platelet aggregation (% OD_{max}) decreased progressively as perfusion continued (Fig.1). However, in the MO group platelet number and ADP induced platelet aggregation stabilized at preperfusion values up to the end of perfusion. Because of too low platelet numbers in PRP ($<$ 75.000/ml), ADP induced platelet aggregation could not be measured in 6 patients of the BO group at the end of perfusion.

Plasma hemoglobin concentration in the BO group increased more than in the MO group during the first 30 minutes of perfusion, whereafter it stabilized. However, after the end of aortic occlusion it increased rapidly and progressively up to 50 and 12 mmol/L in the BO and the MO group respectively at the end of perfusion (Fig.1).



Legend to figure 1:

Mean values and standard errors of the means of platelet number and platelet function (ADP induced platelet aggregation) and plasma hemoglobin concentration, before, during and immediately after perfusion. Platelet number is corrected for hemodilution. Platelet function is expressed as a percentage of preperfusion value.

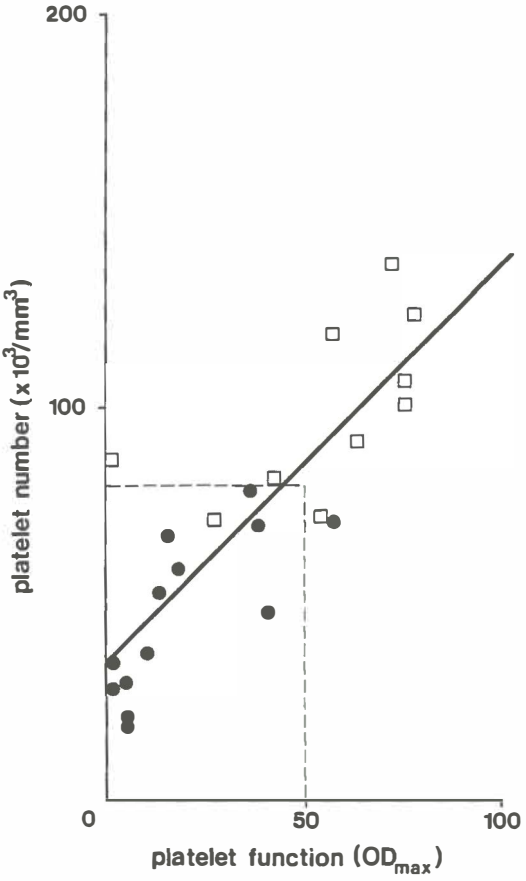
↑ indicates sampling point just before release of the aortic crossclamp.

● =bubble oxygenator

□ =membrane oxygenator

* =$p < 0.05$ (Student's T test)

Postoperative platelet number correlated positively with postoperative ADP induced platelet aggregation (Fig.2). All patients except one, who were perfused with a BO system had low platelet number (< 80.000/ml) corresponding with low ADP induced platelet aggregation (< 50 %). In contrast, all patients except one, who were perfused with an MO system had higher platelet number corresponding with higher ADP induced platelet aggregation.



Legend to figure 2:
Relationship between platelet number and platelet function (ADP induced platelet aggregation). Data within the dotted lines have low platelet number (<80.000/ml) and low platelet function (OD_{max} < 50%). Platelet number is corrected for hemodilution.
Regression equation; y(N) = 35.1 + 1.024x(%), r = 0.824, p < 0.001
● =bubble oxygenator
□ =membrane oxygenator

In both groups postoperative bleeding times increased significantly after perfusion (Fig.3), but were significantly longer in patients perfused with the BO system (Wilcoxon's test, $p < 0.05$). In both groups transfusions of whole blood were equal (mean 2 ± 0.3 U)*, however, in the BO group significantly more units of blood products were transfused (mean 1 ± 0.1 U)* than in the MO group (mean 0 U). Blood loss up to 18 hours after perfusion was not significantly different between the MO group (mean 1293 ± 162 ml)* and the BO group (mean 1162 ± 119)* (Student's T test, $p > 0.05$).

* Mean ± SEM.

DISCUSSION

Cardiotomy suction, implying the aspiration of air along with suction of blood, causes an intensive blood/gas interface at the sucker tip and in the suction lines, inducing turbulences and high shear stresses, consequently damaging platelets (8,10).
It was assumed that the impact of cardiotomy suction on platelets may be so great that it negates the advantage of the MO over the BO. This might explain why some studies observed less platelet damage during MO perfusions (2,3,6,17-19), whereas others did not (20,21). However, lack of standardization of operation type, perfusion time and total volume of cardiotomy return, made exact interpretations difficult. We therefore performed this present study, focussed on CABG operations with long perfusion times averaging 3 hours, known to be accompanied by relatively large volumes of cardiotomy return. In 100 CABG operations (unpublished) we measured total volume

Table 1: Patient and perfusion data (mean ± SEM). Differences between both groups are not significant (Student's T test, $p > 0.05$).

	membrane oxygenator n = 10	bubble oxygenator n = 13
age (years)	57.8 ± 2.3	57.0 ± 2.1
perfusion time (min)	183 ± 12	192 ± 13
aortic occlusion time (min)	111 ± 9	110 ± 9
number of proximal anastomoses	2.0 ± 0.4	2.0 ± 0.6
number of distal anastomoses	4.8 ± 1.0	4.3 ± 1.1
hypothermia temperature (°C)	23.8 ± 1.7	23.7 ± 2.0

of cardiotomy blood return. It varied between 11.6 and 108.0 L., and expressed as a percentage of total blood perfused through the oxygenator it varied between 2.8 and 13.6 %. This total volume of blood return was positively related with perfusion time (regression equation: $y(L) = 16.9 + 0.2x(min)$, $r = 0.46$, $p < 0.05$) and largest mean volume was measured during perfusions of 3-4 hours (61.3 ± 5.9 L)* (12).

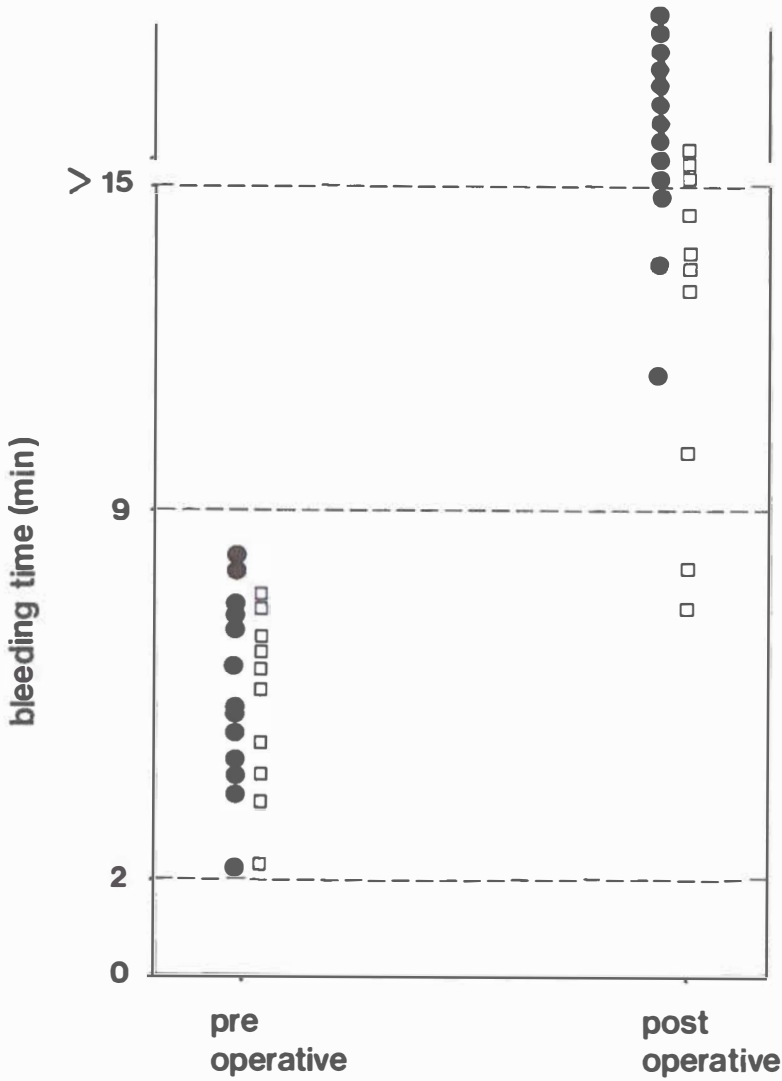
In this present study we found that platelet damage by cardiotomy suction seemed to be relatively small, because after aortic crossclamping platelet number and function decreased only slightly in the BO group, whereas in the MO group both were not affected at all. However, in both groups, as an effect of cardiotomy suction, plasma hemoglobin concentration increased rapidly after aortic crossclamping. This might indicate that erythrocytes are more sensitive to shear stresses induced by suction than platelets are (4,22-25).

In this present study the differences in platelet damage and 18 hours postoperative blood loss and blood transfusions between the BO and MO group were less profound as was found by Van den Dungen (6). That study was also focussed on CABG operations, but with perfusion times averaging 2 hours. Although our present study was performed in an other clinic, we believe that a relative comparison can be made because the same hematological protocol was used by the same group. The smaller differences in platelet damage and consequently in postoperative bleeding tendency between the BO and the MO group in our present study with longer perfusion times than in the study of Van den Dungen, points to the negating effect of cardiotomy suction on platelet damage in the MO perfusions. Despite this negating effect of large volumes of cardiotomy return, there still remains a significant difference in hemolysis, platelet number and platelet function between the MO and the BO group. The effect of the use of the MO on platelet damage and therefore on postoperative hemostasis was reflected in the significantly better postoperative bleeding times in the patients of the MO group.

Like Harker (15,16), we also found a positive correlation between platelet number and function in both groups, nicely corresponding with the duration of the postoperative bleeding time (Fig.2). Almost all patients of the MO group had high platelet number and function corresponding with only slightly prolonged postoperative bleeding times, whereas almost all patients of the BO group had low platelet number and function corresponding with severely prolonged postoperative bleeding times.

So in CABG operations with long perfusion times of mean 3 hours, the MO still exerts significantly less platelet and erythrocyte damage than the BO. However, the differences in platelet damage, postoperative blood loss and blood transfusions between the BO and the MO group in these long perfusions are less pronounced than the differences found in a previous study by Van

* Mean ± SEM.



Legend to figure 3:
Pre- and postoperative bleeding times are related to the type of oxygenator. Normal bleeding time is 2-9 minutes. Differences between both groups are not significant (Wilcoxon's test, $p > 0.05$).

● =bubble oxygenator

□ =membrane oxygenator

den Dungen which also focussed on CABG operations, but with shorter perfusion times of mean 2 hours. This obliteration of the hematological superiority of the MO is most likely explained by the greater volumes of cardiotomy return known to occur during these long perfusions in our study.

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CHAPTER 4

PLATELET DAMAGE AND HEMOLYSIS DURING BUBBLE OXYGENATOR PERFUSION WITH AND WITHOUT ARTERIAL LINE FILTER, COMPARED TO MEMBRANE OXYGENATOR PERFUSION

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ABSTRACT

We determined to what extent a 27 micron depth filter* in the arterial line of a bubble oxygenator (BO) system is responsible for the difference in hemocompatibility between this BO system and a membrane oxygenator (MO) system in which no arterial line filter is used. We studied 3 groups of patients subjected to long perfusions of approximately 3 hours: BO perfusion with (n = 8) and without (n = 8) the arterial line filter and MO perfusion (n = 10) without filter. Platelet and erythrocyte damage were evaluated at 7 sampling points during perfusion. Also pre- and postoperative bleeding times and postoperative blood loss and blood transfusions up to 18 hours after perfusion were determined.
We found that the 27 micron depth filter in the arterial line impairs the hemocompatibility of the BO only to a small extent; the MO remains hematological superior over the BO even when the arterial line filter is absent in the BO circuit.

* Bentley Polyfilter, bypass blood filter PF 427.

INTRODUCTION

An arterial line filter is recommended for cardiopulmonary bypasses with a bubble oxygenator (BO), because a BO system produces a considerable amount of microemboli (1-5). However, an arterial line filter induces turbulences and high shear stresses by the microfenestrations, by which platelets and erythrocytes are damaged (3-8). Furthermore this effect of the arterial line filter is in particular pronounced during long perfusions of over 2 hours and during high flow rates (9). Therefore it might add to the impaired hemocompatibility of the BO system. Because a membrane oxygenator (MO) produces much fewer microemboli than a BO (3,5), the use of an arterial line filter is not indicated here and consequently, one might argue that the difference in hemocompatibility between the BO and the superior MO system, might be partly due to the presence of the arterial line filter in the BO system.
To evaluate this we studied 3 groups of patients all operated for extensive coronary artery bypass procedures with an expected long perfusion time of approximately 3 hours. In two groups a BO perfusion was performed, in one group with the arterial line filter in the extracorporeal circuit and in the other group without. The results for platelet and erythrocyte damage, pre- and postoperative bleeding times and postoperative blood loss and blood transfusions up to 18 hours after perfusion were compared with the results obtained from a third group of patients undergoing an MO perfusion without an arterial line filter.

PATIENTS AND METHODS

All patients gave their informed consent. They were divided at random into three groups. Group 1 consisted of 8 patients undergoing a bubble oxygenator (BO) perfusion (Shiley 100-A HED bubble oxygenator, Shiley Inc., Irvine, California, USA) with the arterial line filter (Bentley Polyfilter, blood bypass filter PF 427, Bentley Lab., Irvine, California, USA). Group 2 consisted of 8 patients indergoing an identical BO perfusion but without the artirial line filter. Group 3 consisted of 10 patients undergoing a membrane oxygenator (MO) perfusion (SciMed spiral coil, SciMed Life Systems Inc., Minneapolis, Minnesota, USA) without the arterial line filter. In all three groups the arterial line filter was used during the priming period of the extracorporeal circuit, in order to remove microemboli from the perfusate (10,11). Thereafter the filter was excluded from the extracorporeal circuit in groups 2 and 3. In all extracorporeal circuits a 27 micron blood filter was incorporated in the venous outlet of the cardiotomy reservoir (Bentley model Q 220-F, Bentley Lab., Irvine, California, USA)(12).

Table 1: Patient and perfusion data (mean ± SEM). Means are not significantly different between the three groups (Student's T test, $p > 0.05$). BO = bubble oxygenator, MO = membrane oxygenator.

	group 1 BO + filter n = 8	group 2 BO - filter n = 8	group 3 MO - filter n = 10
age (years)	54.1 ± 3.5	54.0 ± 1.8	57.8 ± 2.3
perfusion time (min)	195 ± 9	194 ± 15	183 ± 12
number of prox anastomoses	2.0 ± 0	2.3 ± 0.2	2.0 ± 0.5
number of distal anastomoses	5.7 ± 0.3	5.4 ± 0.3	4.8 ± 1.0
hypothermia temperature (°C)	23.5 ± 1.8	24.2 ± 1.7	23.8 ± 1.7
postop. blood loss (ml)	1375 ± 174	1106 ± 131	1326 ± 139
postop. blood transfusions U	3.9 ± 0.7	2.3 ± 0.2	1.9 ± 0.4

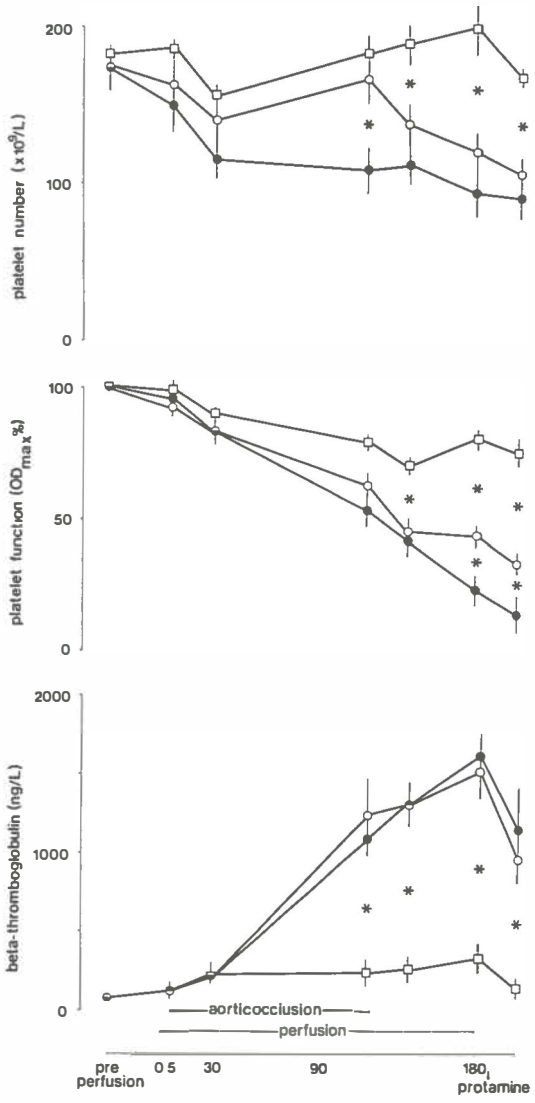
In all cases the circuits were primed with cristalloid solutions (13), and hypothermic low-flow perfusion was performed. During the perfusion no donor blood transfusions were given. Cardioplegia as described by Bleese et al.(14) was used.

Blood samples were taken immediately after induction of anaesthesia, but before sternotomy and heparinization ("preperfusion"), 5 and 30 minutes

after the start of perfusion, just before and 20 minutes after release of the aortic crossclamp, at the end of perfusion and 30 minutes after protamine sulphate administration.
Platelets were counted by an electronic particle counter (Coulter Electronics Inc., Harpenden, Herts, England) in blood collected in EDTA (ethylene diamine tetra-acetic acid). The cell counts were corrected for hemodilution.
Platelet function was expressed by the extent of platelet aggregation, induced by adenosine diphosphate (ADP) in citrated platelet rich plasma (PRP) as described previously(15).
Beta-thromboglobulin (BTG) concentrations in plasma were measured by means of a radio-immuno assay (Radio-Chemical Centre, Amersham, England).
Plasma hemoglobin concentration was determined spectrophotometrically as described by Drabkin (16).
Pre- and postoperative bleeding times were measured in the volar skin of the fore-arm (Simplate II, General Diagnostics, New Jersey, USA)(17). Postoperative blood loss through chest tube drainage and postoperative blood transfusions were measured up to 18 hours after perfusion. Transfusions of blood and blood products were given when the hemoglobin concentration decreased below 6.0 mmol/L or when diffuse bleeding persisted.
The Student's T test or Wilcoxon's test was used for statistical analysis of differences between the groups. Values of $p < 0.05$ were considered to be significant.
All data in text, table and figures are means $\pm$ standard error of the mean.

RESULTS

There were no significant differences between the three groups with respect to age of the patients, perfusion time, number of proximal and distal anastomoses and the temperature during total body hypothermia (Table 1).
In all three groups mean platelet number decreased after the start of perfusion and remained low in the BO group with the arterial line filter (Fig.1). However, in the BO group without the arterial line filter and in the MO group mean platelet number increased again and was significantly higher than in the BO group with the arterial line filter at the end of aortic crossclamping. After release of the aortic crossclamp, mean platelet number decreased again in both BO groups, whereas it continued to increase in the MO group. Mean platelet number in this group was significantly higher as compared to both BO groups from 20 minutes after release of the aortic crossclamp up to 30 minutes after protamine sulphate administration.
During perfusion both BO groups had a more pronounced decrease in platelet function than the MO group (Fig.1). Platelet function was significantly higher in the MO group when compared to both BO groups, from 20 minutes after

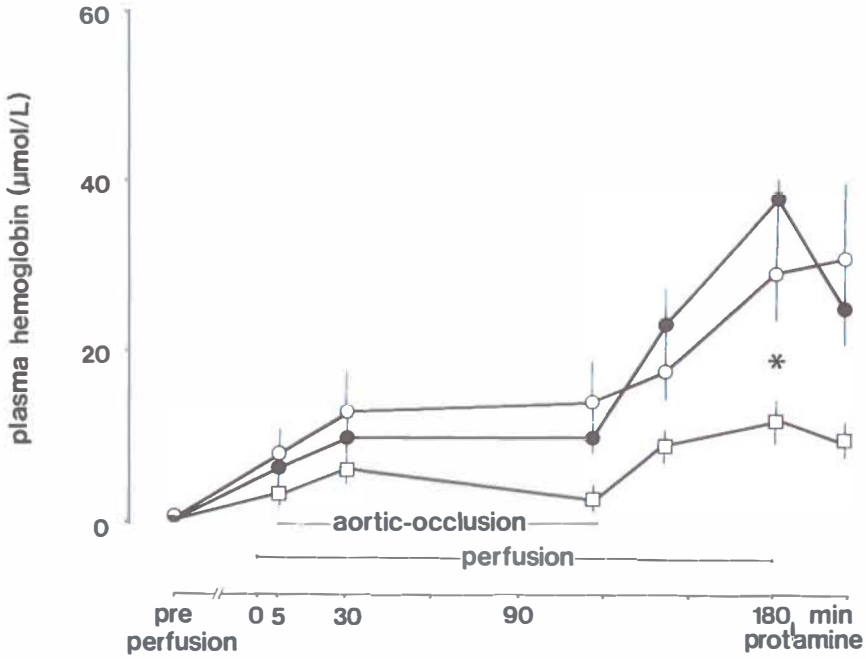


Legend to figure 1:

Mean values and standard errors of the means of platelet number, platelet function (ADP induced platelet aggregation) and beta-thromboglobulin (BTG) plasma concentration, before, during and immediately after perfusion. Platelet number is corrected for hemodilution. Platelet function is expressed as a percentage of preperfusion values.

- ● =bubble oxygenator with arterial line filter
- ○ =bubble oxygenator without arterial line filter
- □ =membrane oxygenator
- * =$p < 0.05$ (Student's T test)

release of the aortic crossclamp up to 30 minutes after protamine sulphate administration.
BTG plasma concentration increased progressively to very high levels at the end of perfusion in both BO groups, whereas it increased only slightly in the MO group (Fig.1). Differences between the MO group and both BO groups were highly significant ($p < 0.001$) after 120 minutes of perfusion.
Plasma hemoglobin concentration increased after the start of perfusion in all three groups and stabilized thereafter up to end of aortic crossclamping (Fig.2). However, after release of the aortic crossclamp it increased further in all three groups. Only at the end of perfusion did plasma hemoglobin concentrations differ significantly between the BO group with the arterial line filter and the MO group.
Postoperatively bleeding times were significantly increased in all three groups, but did not differ significantly between the three groups (Fig.3). Also blood

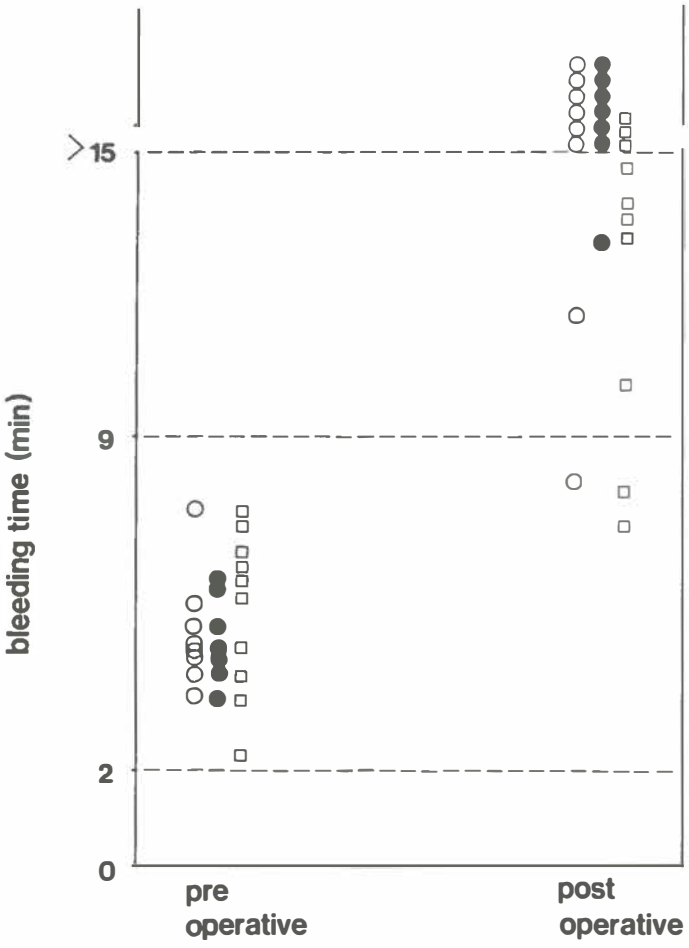


Legend to figure 2:
Mean values and standard errors of the means of plasma hemoglobin, before, during and immediately after perfusion. Only at the end of perfusion, mean concentration of plasma hemoglobin differred significantly between the BO group with the arterial line filter and the MO group.
● =bubble oxygenator with arterial line filter
○ =bubble oxygenator without arterial line filter
□ =membrane oxygenator
* =$p < 0.05$ (Student's T test)

loss and donor blood transfusions, measured up to 18 hours after perfusion, did not differ significantly between the three groups (Table 1).

DISCUSSION

The results of this study indicate that the arterial line filter hardly contributed to the damaging effects of a BO system on platelets and erythrocytes, because



Legend to figure 3:
Pre- and postoperative bleeding times related to the type of oxygenator used during perfusion. Normal bleeding time is 2-9 minutes. Differences between the three groups are not significant (Wilcoxon's test, $p > 0.05$).
- ● =bubble oxygenator with arterial line filter
- ○ =bubble oxygenator without arterial line filter
- □ =membrane oxygenator

when the arterial line filter was added to the BO system, only platelet function impaired slightly, although significantly. All other indicators of blood cell damage, platelet number, beta-thromboglobulin (BTG) plasma concentration, hemolysis, postoperative bleeding times, postoperative blood loss and blood transfusions up to 18 hours after perfusion, remained similar in both BO groups. So the arterial line filter impaired the hemocompatibility of the BO system only to a small extent.

In this study the hemocompatibilty of both BO systems was compared with that of the MO system, because it was suggested that the difference in hemocompatibility might be due to the arterial line filter(3-9), which is not used in our MO system (13,15,18). We found, however, that the MO is still hematological superior over the BO even in the absence of the arterial line filter in the BO system. This is demonstrated by the significantly higher platelet numbers, a better platelet function, lower BTG plasma concentrations and less hemolysis in the MO group. However, in the last part of the perfusion period, this hematological superiority is obscured by cardiotomy suction (2,3,17). This became obvious after release of the aortic crossclamp when cardiotomy suction was intensified, as was demonstrated by a steep increase in plasma hemoglobin concentration in all three groups. The simultaneity of this increase in all three groups in particular suggests that this damage was due to cardiotomy suction. This source of blood damage was similar in all three groups, and might also explain that no differences between the three groups were found in bleeding times, postoperative blood loss and blood transfusions.

In conclusion, we found that the 27 micron depth filter in the arterial line of the BO system impaired the hemocompatibility of the BO system only to a small extent, even in long perfusions of approximately 3 hours.

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CHAPTER 5

REDUCED PLATELET ACTIVATION AND IMPROVED HEMOSTASIS AFTER CONTROLLED CARDIOTOMY SUCTION DURING CLINICAL MEMBRANE OXYGENATOR PERFUSIONS

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ABSTRACT

Platelet damage and postoperative blood loss are less severe after cardiopulmonary bypass performed with a membrane oxygenator (MO) than with a bubble oxygenator (BO). However this advantage of the MO can be partly negated by the platelet damage caused by cardiotomy suction, which implies the aspiration of air along with suction of blood (US).
In order to reduce platelet damage by cardiotomy suction, we developed an automatic controlled cardiotomy suction system by which the aspiration of air was prevented (CS). We evaluated platelet damage in a group of 28 patients (US, n = 13; CS, n = 15) and studied the relationship between increasing volumes of cardiotomy suction and postoperative blood loss in a second group of 80 patients (US, n = 47; CS, n = 33). All patients underwent a coronary artery bypass grafting operation (CABG), using an MO.
We measured significantly lower beta-thromboglobulin concentrations during perfusions of approximately 2 hours and a tendency of shorter postoperative bleeding times if controlled cardiotomy suction was used. There were no significant differences between controlled and uncontrolled cardiotomy suction in platelet number and platelet function (ADP-induced platelet aggregation). However, in the controlled suction group 18 hours postoperative blood loss was significantly less than in the uncontrolled suction group when the total volume of cardiotomy suction exceeded 65 L, which corresponded with perfusion times of over 3 hours.
In conclusion, prevention of the aspiration of air along with suction of blood significantly reduced platelet activation and postoperative blood loss, particulary when large volumes of blood were aspirated.

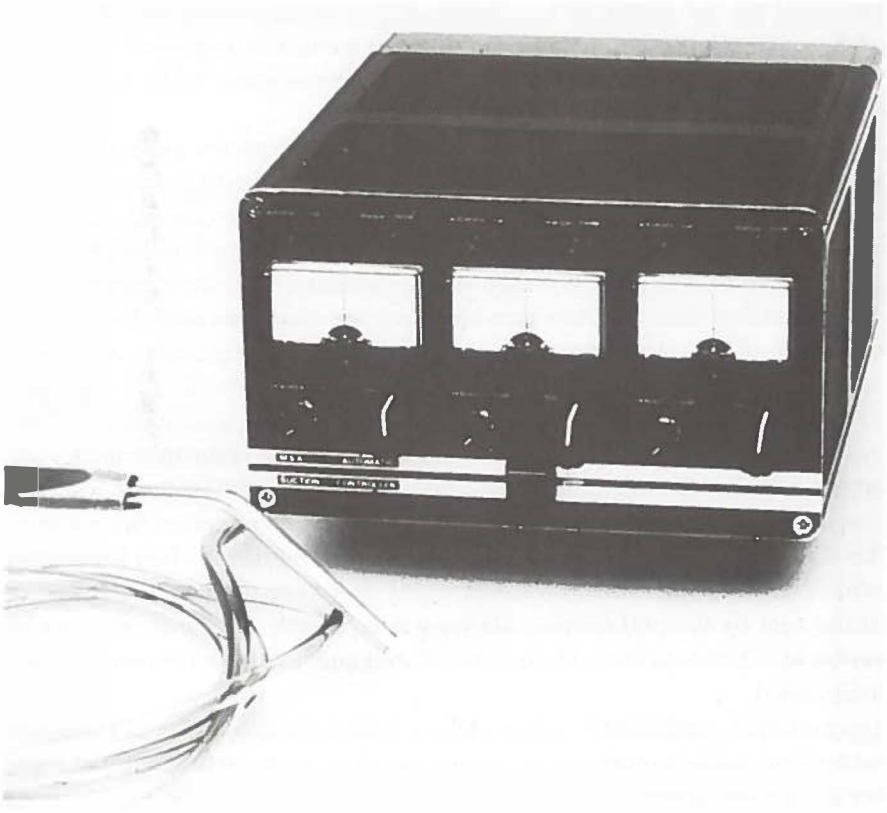
INTRODUCTION

Membrane oxygenators are introduced in the extracorporeal circuit during cardiopulmonary bypass operations, in order to reduce platelet damage, which is mainly caused by the direct blood/gas interface created in the bubble oxygenator (1-3). However, during bypass cardiotomy suction also damages platelets, due to the aspiration of air along with suction of blood, which consequently can partly obscure the hematological advantage of the membrane oxygenator (4-7).
Therefore we developed an automatic controlled cardiotomy suction system to prevent the aspiration of air along with suction of blood, and evaluated platelet damage during membrane oxygenator perfusions in coronary artery bypass grafting operations.
To determine the effect of this controlled suction system on platelet damage,

we measured platelet number, platelet function, plasma concentration of beta-thromboglobulin and bleeding time, before, during and after perfusion in a group of 28 patients.
To determine the effect of controlled suction on postoperative hemostasis, we studied the relationship between increasing total volumes of cardiotomy suction and postoperative blood loss in an extended group of 80 patients.

PATIENTS AND METHODS

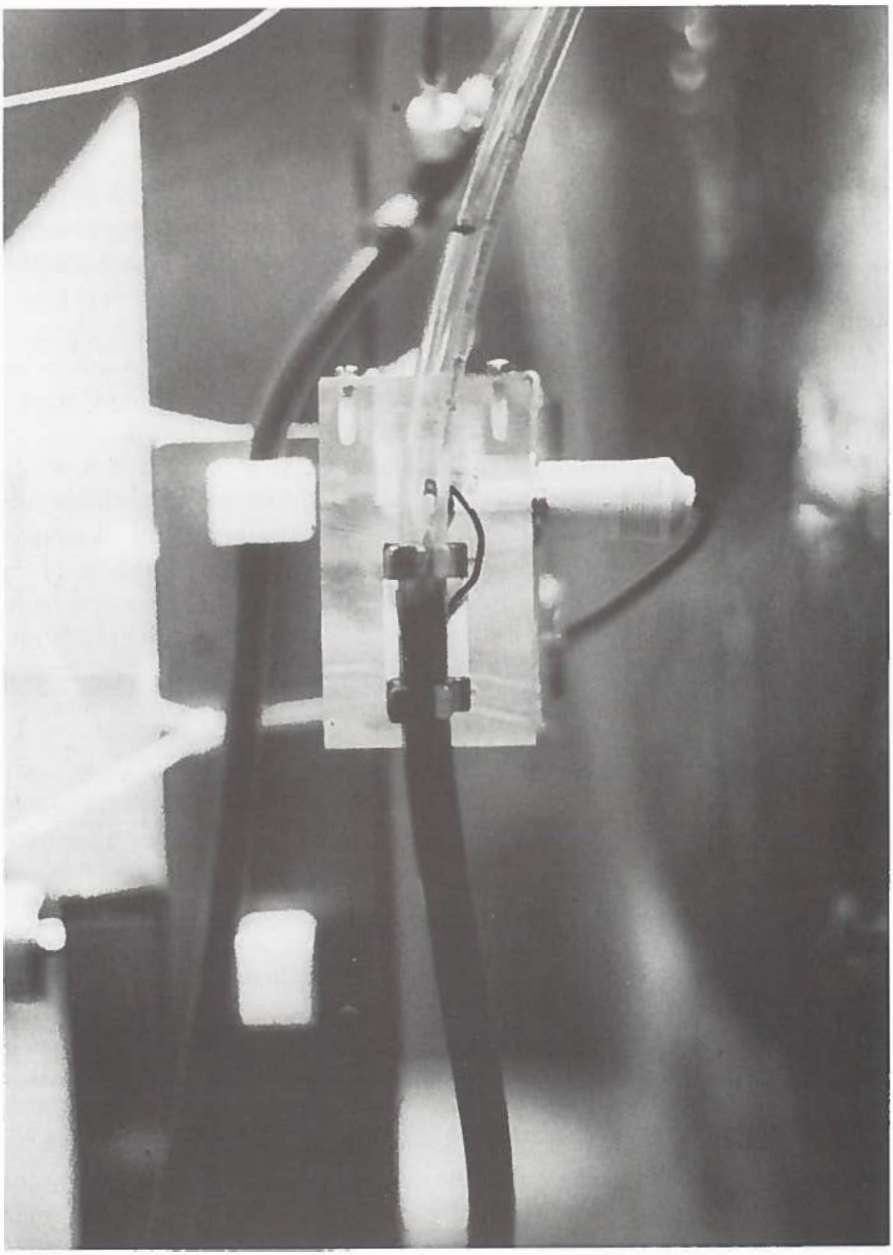
This prospective study was focussed on patients undergoing a coronary artery bypass grafting operation (CABG). Patients pretreated with drugs that are



Legend to figure 1:
Pericardiotomy sucker and automatic controlled suction device. Both electrodes at the sucker tip are connected to electric wires, which are completely isolated in the wall of the ½ inch PVC tubing and connected to the suction device.

known to cause platelet damage were excluded from this study. Informed consent was obtained from each patient.
The automatic controlled cardiotomy suction (CS) system consists of a special pericardiotomy sucker and an automatic controlled suction device (Medical Scientific Application, Den Bosch, The Netherlands) by which the aspiration of air along with suction of blood is prevented (Fig.1). This device, meeting the safety requirements, regulates the revolutions per minute (rpm) of the roller pump of the pericardiotomy sucker, according to the blood level in the pericardium that is sensed by two titanium electrodes, which are located just above the tip of the pericardiotomy sucker. These two electrodes are coated with titanium oxide and are supplied with a high frequency voltage (30 kHz). The current through these electrodes on the tip of the pericardiotomy sucker, is directly proportional to the blood level in between them. This current is the signal for the automatic controlled suction device to regulate the r.p.m. of the roller pump, thus keeping the blood at a constant negligibily low level. When a dry operation area is needed, the device can immediately be switched to "manual".
This automatic controlled suction device also prevents the aspiration of air along with suction of blood in the vent of the left ventricular decompression line (Fig.2). In the conventional set-up the perfusionist can determine the degree of left ventricular decompression, as indicated by the height of the column of blood in the open limb of a manometer-like arrangement in the decompression line, and can provide adequate decompression by adjusting the r.p.m. of the roller pump, or by gravity. However, in practice, continuous adjustment of left ventricular decompression is not possible and aspiration of air via the vent occurs. This aspiration of air is prevented when two modified electrodes are mounted around the open limb of the manometer-like arrangement of the left ventricular vent. Just as in the controlled pericardiotomy sucker, the automatic controlled suction device regulates the r.p.m. of the roller pump, maintaining a constant blood level in the open limb of the vent. The modified electrodes can be easily moved up or down the open limb of the vent by the perfusionist, allowing adequate decompression of the left ventricle. Thus aspiration of air is prevented and adequate decompression is maintained.
Uncontrolled cardiotomy suction (US) is called the conventional method of cardiotomy suction implying the aspiration of air along with suction of blood via the pericardiotomy sucker.
Preoperatively all patients were anticoagulated with acenocoumarol, which was replaced by heparin (2 x 5000 IU sc) two days before the operation. Administration of heparin was stopped the night before the operation. Anticoagulation just before cannulation of the aorta was induced with heparin (300 IU/kg) and supplemented with heparin (100 IU/kg) each hour of perfusion. Heparin was neutralized with protamine hydrochloride (300 IU/kg)

within 30 minutes after the end of perfusion. In both groups the extracorporeal circuit consisted of a membrane oxygenator (SciMed, model 3500-2A, SciMed



Legend to figure 2:
Electrodes surround the open limb of the left ventricular decompression line. The electrodes are connected to the suction device.

Life Systems Inc., Minneapolis, Minnesota, USA), a venous reservoir, a cardiotomy reservoir (Dideco, model D 641, with a 40 micron filter, Dideco s.p.a., Mirandola, Italy) and four roller pumps (Dreissen, Hellevoetsluis, The Netherlands) with ¼ inch ID PVC tubing: one roller pump was used for arterial return, one for decompression of the left ventricle (Sarns 10610, 18 Fr, Sarns Inc., Ann Arbor, Michigan, USA), one for cardiotomy suction and one for venting of the aortic root (DLP, 7 Fr, Watson SW, Grand Rapids, Michigan, USA).

Total volume of blood return to the extracorporeal circuit was measured by means of a blood flow probe in the blood outlet of the cardiotomy reservoir and connected to a blood flow integrator unit (Nycotron, model 376/393, Drammen, Norway). The extracorporeal circuit was primed with 2 L of a plasma substitute (Gelifundol, Biotest Pharma, Dreieck, West-Germany). Arterial flow rates were 2.4 $L/m^2/min$ during hypothermia. The solutions for cardioplegia and continuous external cooling of the heart were mostly aspirated in a separate reservoir and returned to the patient bit by bit.

Platelet damage was evaluated in 28 patients (CS, n = 15; US, n = 13). Blood samples were taken immediately after induction of anaesthesia, but before sternotomy and heparinization (= preperfusion), 5 and 30 minutes after the start of perfusion, just before and 20 minutes after release of the aortic crossclamp, at the end of perfusion and 30 minutes after protamine hydrochloride administration. Blood samples for measurement of beta-thromboglobulin (BTG) plasma concentration were carefully drawn from a short catheter in the radial artery and were immediately cooled in a tube containing an antiplatelet reagent and EDTA (ethylene diamine tetra-acetic acid). BTG concentrations in the plasma were measured by means of a commercial radioimmuno assay (Radio Chemical Centre, Amersham, England)(8,9). Platelets were counted by an electronic particle counter (Coulter Electronics Inc., Hia Leab, Florida, USA) in blood collected in EDTA. Platelet aggregation was induced by ADP (adenosine diphosphate) in platelet rich plasma (PRP)(10,11). Citrated PRP was stored at room temperature and was tested approximately 60 minutes after sampling. Platelet number in PRP was adjusted to 100.000/ml in each sample. Platelet aggregation was assessed by measurement of the OD_{max}, which is the maximal procentual change in optical density of PRP after ADP induced platelet aggregation, compared to platelet poor plasma (PPP). Only in the first sample (preperfusion), various doses of ADP were tested to induce platelet aggregation in order to find that ADP concentration which resulted in a ± 65 % change of the maximal achievable decrease in optical density ("second wave")(12). This ADP concentration was used to induce platelet aggregation in all following samples obtained during perfusion.

Preoperative and postoperative bleeding times were determined in the volar skin of the fore-arm (Simplate II, General Diagnostics, New Jersey,

USA)(13). Standard laboratory procedure was used for determination of plasma hemoglobin (14).
Postoperative hemostasis was evaluated in 80 patients (CS, n = 33; US, n = 47), by measurement of postoperative blood loss through chest tube drainage up to 18 hours after the end of perfusion. Patients were divided in three groups according to the total amount of cardiotomy return measured during perfusion; less than 45 L, 45 to 65 L and more than 65 L.
The Student's paired T test and the Wilcoxon's test were used for statistical analysis of differences between the groups. Values of $p < 0.05$ were considered to be significant.

RESULTS

I: The effect of uncontrolled (US) and controlled (CS) cardiotomy suction on platelet alterations.

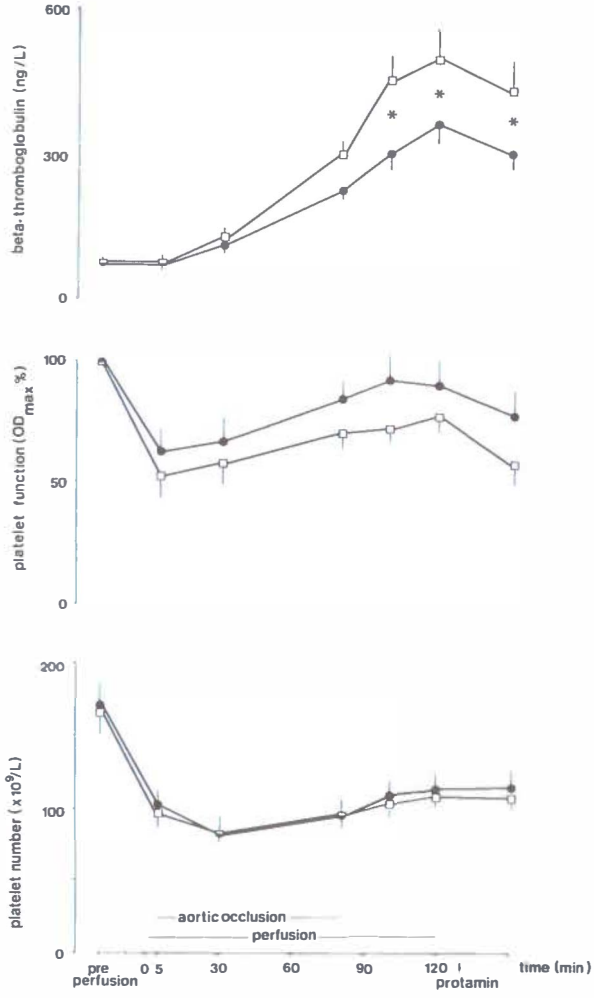
There were no significant differences between the two groups in age, perfusion time, number of proximal and distal anastomoses, total volume of cardiotomy suction and body hypothermia. (Table 1).
During aortic crossclamping, BTG levels increased in both groups. In this period only minimal cardiotomy suction was generally required. After aortic crossclamping, when more cardiotomy suction was needed, BTG levels increased rapidly in the US group, but increased only slightly in the CS group. Significant differences between the two groups were observed from 20 minutes after aortic crossclamping up to 30 minutes after protamine hydrochloride administration (Fig.3).

Table 1: Patient and perfusion data from the study on platelets (mean ± SEM).

	controlled suction n = 15	uncontrolled suction n = 13
age (years)	54.4 ± 1.9	52.4 ± 1.7
perfusion time (min)	124 ± 12	130 ± 13
number of proximal anastomoses	1.9 ± 0.2	1.7 ± 0.1
number of distal anastomoses	3.7 ± 0.3	3.4 ± 0.3
total volume of card suction(L)	45.3 ± 3.3	43.4 ± 4.4
total body hypothermia (°C)	26.7 ± 0.3	26.8 ± 0.3

In both groups ADP induced platelet aggregation decreased immediately after start of perfusion, but it increased slightly thereafter up to 20 minutes

after aortic crossclamping. After protamine hydrochloride administration, ADP induced platelet aggregation decreased to 75 and 55 % of preperfusion value in the CS and the US group respectively (Fig.3). Although ADP induced platelet aggregation was consistently better in the CS group, mean differences between both groups were not significant.



Legend to figure 3:

Mean values and standard errors of the mean of beta-thromboglobulin plasma concentration (BTG), platelet function (ADP induced platelet aggregation) and platelet number, before, during and immediately after perfusion. Platelet function is expressed as a percentage of preperfusion value.

- ● =controlled suction
- □ =uncontrolled suction
- * =$p < 0.05$ (Student's T test)

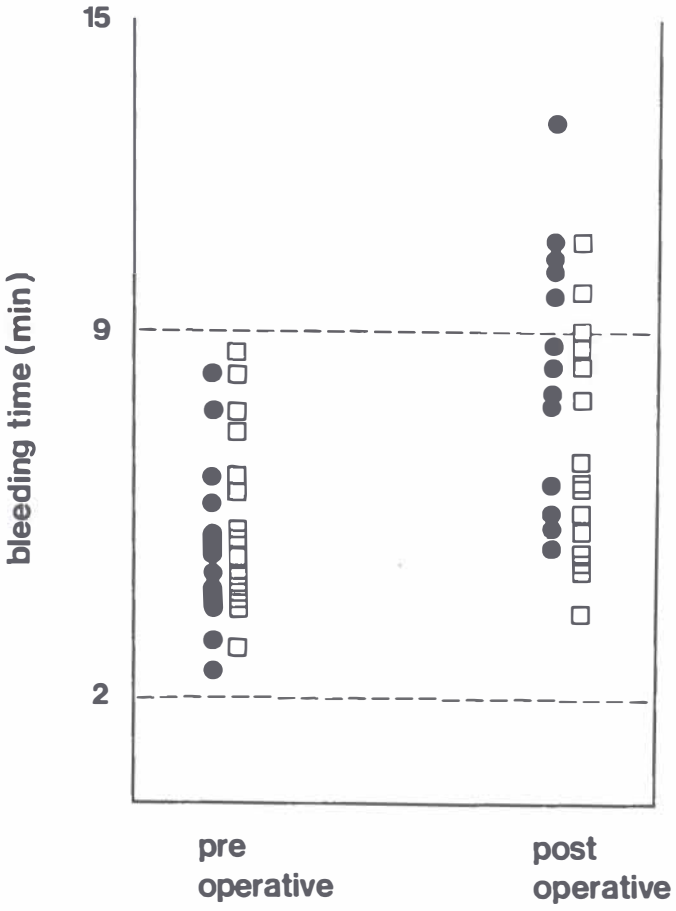
In both groups platelet number decreased substantially after start of perfusion, which was almost completely due to hemodilution. It recovered only slightly during the perfusion period. Platelet number was not affected by protamine hydrochloride administration. Differences between both groups were not significant (Fig.3).
In both groups bleeding times were significantly increased after the operation. However, in the US group postoperative bleeding times were prolonged to more than nine minutes in five out of thirteen patients, whereas in the CS group postoperative bleeding times were prolonged to more than nine minutes in only two out of fifteen patients (Fig.4); however, these differences were not significant.
Mean plasma hemoglobin concentration increased slightly in both groups to 268 mg % in the US group and to 235 mg % in the CS group at the end of perfusion. Differences between the means of both groups were not significant at any sampling point.

II: The effect of increasing volumes of uncontrolled (US) and controlled (CS) cardiotomy suction on postoperative blood loss.
In the US group an increase in the total volume of cardiotomy suction caused a significant increase in postoperative blood loss, measured up to 18 hours after the stop of perfusion. However, in the CS group an increase in the total volume of cardiotomy suction caused only a slight but not significant increase in postoperative blood loss. Greatest postoperative blood loss was measured in the US group and differed significantly from the CS group when mean total volume of cardiotomy suction exceeded 65 L, corresponding with perfusion times of approximately over 3 hours (Fig.5).

DISCUSSION

Impaired hemostasis after cardiopulmonary bypass is mainly due to platelet damage (15-20). The bubble oxygenator (BO) used during cardiopulmonary bypass has been recognized as a main source of this platelet damage (1,21), which can be reduced by using a membrane oxygenator (MO)(2,3).
However, also cardiotomy suction is known to be a source of platelet damage due to the aspiration of air along with suction of blood (4,5), causing an intensive blood-gas contact at the sucker tip and in the suction lines, inducing turbulences and high shear stresses which damage the blood elements. Wright (6) demonstrated that during his experiments shear stresses of 140 Nm/m^2 to 300 Nm/m^2 are generated depending on the amount of aspirated air, which are able to damage platelets. Goldsmith (22) also showed the deleterious effect of high shear stresses on platelet aggregation and platelet release reaction. So cardiotomy suction might obscure the reduction in platelet damage that was obtained by using the MO.

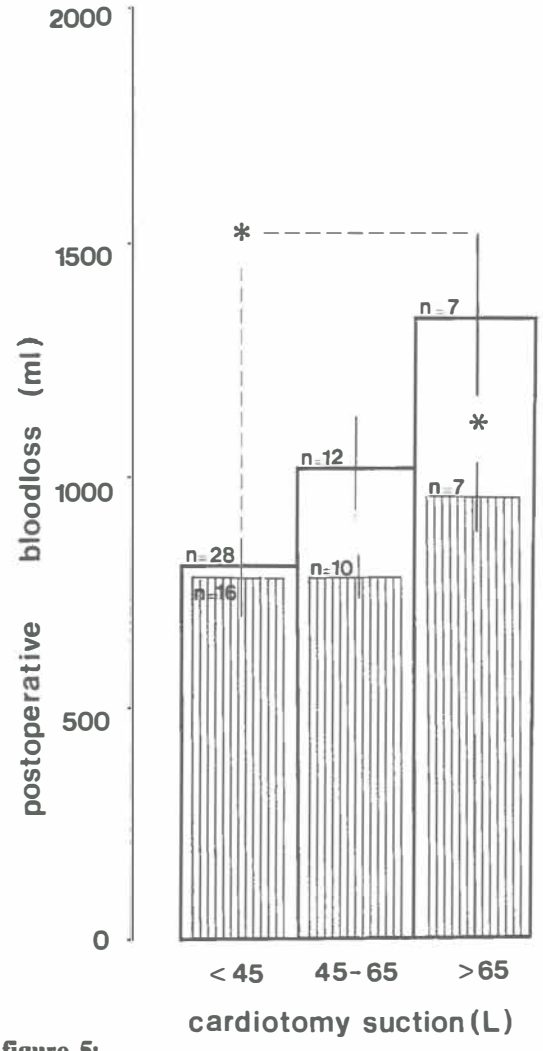
In order to minimize platelet damage by cardiotomy suction, we developed an automatic controlled suction system, which virtually eliminates the aspiration of air along with suction of blood. In the experimental set-up de Jong



Legend to figure 4:
Pre- and postoperative bleeding times related to the method of cardiotomy suction. Normal bleeding time is 2-9 minutes. Differences between both groups are not significant ($p > 0.05$, Wilcoxon's test).
□ =controlled suction
● =uncontrolled suction

(3) demonstrated in MO perfusions on dogs, that controlled cardiotomy suction reduced platelet damage and improved postoperative hemostasis to the same extent as was obtained in an MO perfusion without cardiotomy suction. However, when uncontrolled cardiotomy suction was used during an MO perfusion, platelet damage increased and postoperative hemostasis

impaired to the same extent as during a BO perfusion. He also found significantly less erythrocyte damage in dogs perfused with the MO in conjuction with controlled cardiotomy suction.
In the present study we introduced this automatic controlled suction system in clinical MO perfusions, so platelet and erythrocyte damage were expected



Legend to figure 5:
Mean values and standard errors of the mean of postoperative blood loss after increasing total volumes of cardiotomy suction.
||| =controlled suction
□ =uncontrolled suction
* =$p < 0.05$ (Student's T test)

to be reduced and postoperative hemostasis was expected to be improved when compared to uncontrolled cardiotomy suction.

In the study on platelets, performed with a perfusion time of approximately 2 hours, we found that in the perfusion period after aortic crossclamping, controlled cardiotomy suction significantly reduced beta-thromboglobulin (BTG) plasma concentrations, indicating that platelets were less activated by controlled cardiotomy suction. This reduction in platelet activation was not reflected in an increase in platelet number, however, ADP-induced platelet aggregation was consistently improved and postoperative bleeding times were shorter in the controlled suction group.

In this platelet study on coronary artery bypass grafting operations, with perfusion times of approximately 2 hours and with a limited total volume of cardiotomy suction (Table 1), no significant differences were measured between the uncontrolled and controlled suction group in postoperative blood loss, known as an indicator of overall hemostasis. Also in hemolysis no differences were noted, pointing to the fact that these limited volumes of cardiotomy suction do not significantly affect erythrocytes, as was also indicated by the small differences between both groups in regard to platelet damage. This is in agreement with the observations of blood loss in the group of 80 patients in which we studied the relationship between increasing total volumes of cardiotomy suction and postoperative blood loss. We found no significant differences in postoperative blood loss between the controlled and uncontrolled suction group in perfusions shorter than 3 hours. However, if perfusion times were longer, corresponding with larger total volumes of cardiotomy suction (< 65 L), we measured a significant increase in postoperative blood loss in the uncontrolled suction group, whereas only a slight but insignificant increase was measured in the controlled suction group. Differences between both were significant when the total volume of cardiotomy suction exceeded 65 L and mean perfusion times were approximately 3 hours or longer. These large volumes of cardiotomy suction do not frequently occur in coronary artery bypass grafting operations, but they are more common in corrections of cyanotic heart diseases and in multiple valve replacement operations (23).

From our findings in this clinical study we conclude that controlled cardiotomy suction significantly reduces platelet activation during membrane oxygenator perfusions in coronary artery bypass grafting operations and significantly improves postoperative hemostasis, in particular when large volumes of cardiotomy suction occur. In operations requiring these large volumes of cardiotomy suction, such as in coronary artery bypass grafting operations with long perfusion times, in multiple valve replacement operations or in corrections of cyanotic heart diseases, the hematological advantage of the membrane oxygenator can be improved when in addition controlled cardiotomy suction is used.

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CHAPTER 6

CONTROLLED CARDIOTOMY SUCTION DURING CLINICAL BUBBLE OXYGENATOR PERFUSIONS

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ABSTRACT

Cardiotomy suction causes platelet damage and hemolysis due to air aspiration along with blood suction (uncontrolled suction = US). However, prevention of air aspiration (controlled suction = CS) reduces platelet damage and hemolysis and improves postoperative hemostasis, as we reported only for membrane oxygenator (MO) perfusions.
We now evaluated CS during bubble oxygenator perfusions (BO). We studied 3 groups of patients subjected to extracorporeal circulation: BO with CS (n = 10), BO with US (n = 8) and MO with US (n = 10).
When CS was used during BO perfusions we found that only hemolysis was significantly reduced, if compared to BO perfusions with US. Despite the use of CS during BO perfusions, platelets were still significantly better preserved during MO perfusions in which US was used. This was indicated by higher platelet number, higher ADP-induced platelet aggregation, lower beta-thromboglobulin plasma concentration, during and immediately after MO perfusions. Blood loss and blood transfusions up to 18 hours after perfusion were not significantly different between the three groups.
We conclude that the platelet preserving capacity of CS is completely lost by the platelet damaging effect of the BO. However, the reduction in hemolysis is well maintained.

INTRODUCTION

Several studies have shown that membrane oxygenators have a superior hemocompatibility when compared to bubble oxygenators (1-5). In recent studies we have shown that the hemocompatibility during membrane oxygenator perfusions could be further improved by replacing the conventional method of cardiotomy suction (uncontrolled suction) by controlled suction, in which the simultaneous aspiration of air along with suction of blood was prevented (6,7). These effects were only demonstrated during membrane oxygenator perfusions and we wondered if the hemocompatibility of the bubble oxygenator also could be improved by controlled cardiotomy suction.
To study this effect we used the automatic controlled cardiotomy suction device by which the aspiration of air along with suction of blood is prevented (6).
We studied 3 groups of patients all operated upon for extensive coronary revascularization procedures, during which large volumes of cardiotomy suction occur (1). In two groups a bubble oxygenator perfusion was performed, in one group with uncontrolled and in the other with controlled cardiotomy suction. The results were compared with those obtained from patients undergoing a membrane oxygenator perfusion during which uncontrolled cardiotomy suction was used.

PATIENTS AND METHODS

Preoperatively, patients were divided at random into three groups. Group 1 consisted of 8 patients undergoing a bubble oxygenator perfusion (Shiley 100-A HED bubble oxygenator, Shiley Inc., Irvine, California, USA) with uncontrolled cardiotomy suction, Group 2 consisting of 10 patients undergoing a bubble oxygenator perfusion with controlled cardiotomy suction and Group 3 consisting of 10 patients undergoing a membrane oxygenator perfusion (SciMed spiral coil, SciMed Life Systems Inc., Minneapolis, Minnesota, USA), with uncontrolled cardiotomy suction.

The automatic controlled cardiotomy suction system consisted of a special pericardiotomy sucker as described elsewhere (6,7). By this system aspiration of air is prevented, and this method is therefore called "controlled" cardiotomy suction. This is in contrast to the conventional method of cardiotomy suction, which implies aspiration of air together with suction of blood. We call this method "uncontrolled" cardiotomy suction. In all cases the left ventricle was drained by gravity via a transatrial drainage system which aspirated no air.

In the bubble oxygenator system the arterial line filter (Bentley Polyfilter, blood bypass filter PF 427, Bentley Lab., Irvine, California, USA) was used only during the priming period of the extracorporeal circuit and it was excluded just before the start of perfusion (8). Both oxygenator systems were clear primed. Cardioplegia as described by Bleese was used (9).

Platelets were counted by an electronic particle counter (Coulter Electronics Inc., Hia Leah, Florida, USA) on blood collected in EDTA (ethylene diamine tetra-acetic acid). Cell counts were corrected for hemodilution. Platelet function was expressed by the extent of platelet aggregation, induced by adenosine diphosphate (ADP) in platelet rich plasma (PRP) (10). Citrated PRP was stored at room temperature and was tested approximately 60 minutes after sampling. Platelet number in each sample was adjusted to 75,000-100,000/ml. Platelet aggregation was assessed by the measurement of the OD_{max}, which is the maximal percentage change in optical density of PRP after ADP-induced platelet aggregation. In the "preperfusion" sample only, various doses of ADP were tested to induce platelet aggregation, in order to find the ADP concentration which resulted in a $\pm$ 65 % change of the maximal achievable decrease in optical density ("second wave") of PRP (11). This ADP concentration was used to induce platelet aggregation in all following samples obtained during perfusion.

Blood samples for measurements of beta-thromboglobulin (BTG) plasma concentration were cooled immediately in a tube containing an antiplatelet reagent and EDTA. BTG plasma concentrations were measured by means of a commercial radio-immuno assay (Radio-Chemical Centre, Amersham, England).

Plasma hemoglobin was determined by a method as described by Drabkin (12).
Pre- and postoperative bleeding times were determined in the volar skin of the fore-arm (Simplate II, General Diagnostics, New Jersey, USA)(13). Postoperative blood loss through chest tube drainage and postoperative blood transfusions were measured up to 18 hours after the end of perfusion. Transfusions of whole blood or blood products were given when hemoglobin concentration was decreased below 6 mmol/L, or when diffuse bleeding persisted.
The Student's T test or Wilcoxon's test were used for statistical analysis of differences between the groups. Values of $p < 0.05$ were considered to be significant.
All data in text, table and figures are means ± standard errors of the mean.

RESULTS

There were no significant differences between the patients of the three groups in age, perfusion and aortic crossclamping time, number of proximal and distal anastomoses and total body hypothermia (Table 1).

Table 1: Patient and perfusion data (mean ± SEM). Mean differences between the three groups are not significant (Student's T test, $p > 0.05$). BO = bubble oxygenator, MO = membrane oxygenator, US = uncontrolled suction, CS = controlled suction.

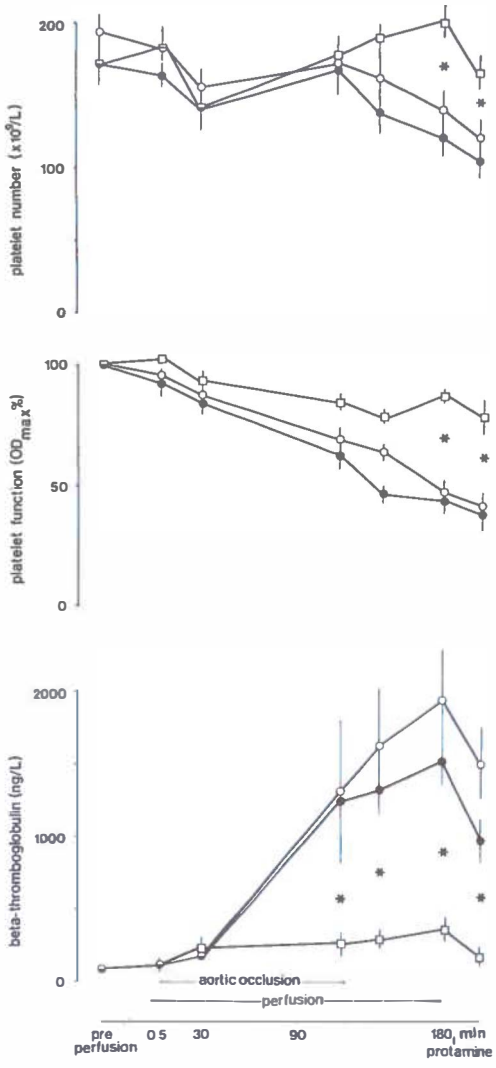
	group 1 BO + US n = 8	group 2 BO + CS n = 10	group 3 MO + US n = 10
age (years)	54.0 ± 1.8	57.7 ± 3.1	57.8 ± 2.3
perfusion time (min)	194 ± 15	180 ± 16	183 ± 12
aortic occlusion time (min)	194 ± 8	105 ± 9	111 ± 9
number of prox. anastomoses	2.3 ± 0.2	2.4 ± 0.2	2.0 ± 0.5
number of distal anastomoses	5.4 ± 0.3	5.1 ± 0.1	4.8 ± 1.0
hypothermia temp. (°C)	24.2 ± 1.7	23.9 ± 0.9	23.8 ± 1.7
postop. blood loss (ml)	1106 ± 131	1079 ± 96	1326 ± 139
postop. blood transf. (U)	2.3 ± 0.2	1.9 ± 0.2	1.9 ± 0.4

In all three groups mean platelet number decreased significantly after start of perfusion, but recovered thereafter up to the end of aortic crossclamping. However, after release of the aortic crossclamp platelet number decreased again in both BO groups while they continued to increase in the MO group. At the end of perfusion they were significantly higher in the MO group (Fig.1).
ADP-induced platelet aggregation decreased progressively and significantly

during perfusion in both the BO groups, whereas in the MO group it decreased slightly but not significantly (Fig.1).
BTG plasma concentrations increased progressively to very high levels at the end of perfusion in both BO groups, whereas in the MO group BTG plasma concentration increased only slightly (Fig.1).
In BO group 1 (+ US) plasma hemoglobin concentration increased progressively during perfusion and the highest levels were reached 30 minutes after protamine sulphate administration. In this group it was significantly higher than in both the BO group 2 (+ CS) and MO group 3 (+ US), at the end of perfusion and at 30 minutes after protamine sulphate administration (Fig.2).
Bleeding times increased significantly postoperatively in all three groups, but did not differ significantly between the three groups (Fig.3).
Blood loss and donor blood transfusions up to 18 hours after the end of perfusion did not differ significantly between the three groups (Table 1).

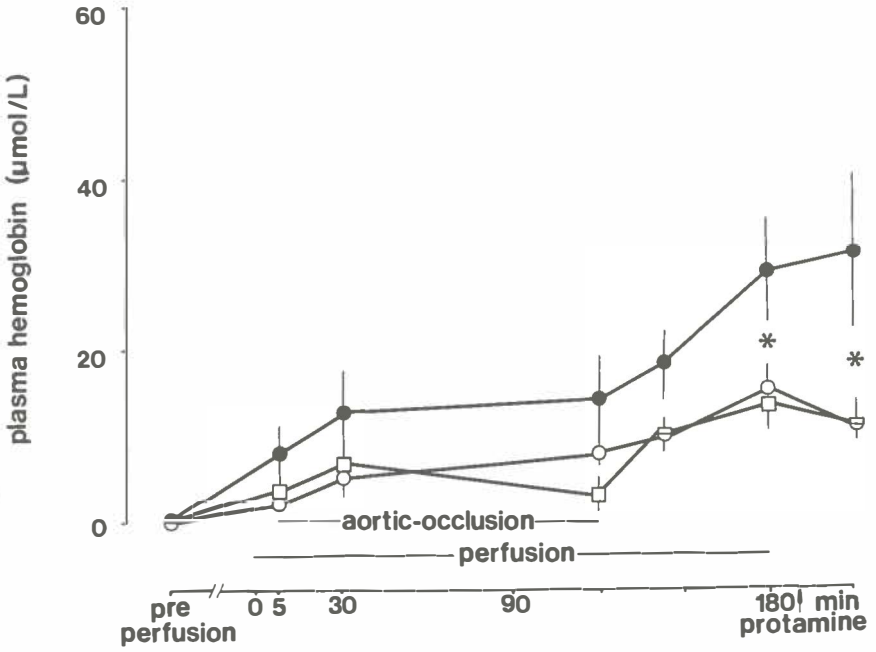
DISCUSSION

Platelet damage is an important consequence of cardiopulmonary bypass and results in an impaired postoperative hemostasis (14-17). In previous studies it was demonstrated that platelet damage and also hemolysis were substantially reduced if the bubble oxygenator was replaced by a membrane oxygenator (1-5). However, due to the aspiration of air along with suction of blood (= uncontrolled suction), the cardiotomy suction system masks, at least partly, these reductions in platelet damage and hemolysis during perfusions with a membrane oxygenator system. This is probably caused by the turbulences and high shear stresses which are induced by air aspiration and which are generated at the sucker tip and in the suction lines, consequently damaging blood cells (18-20). This effect of uncontrolled suction is pronounced in particular during operations in which large volumes of cardiotomy suction occur, like in corrections of cyanotic heart diseases in children (21), or, as we found, in coronary artery bypass grafting operations (CABG) of 3 hours or longer (1). During these long CABG operations of approximately 3 hours, total volume of blood return to the cardiotomy reservoir is approximately 6.1 % (= 61.3 ± 5.9 L) of that passing through the extracorporeal circuit. In order to reduce the platelet and erythrocyte damaging effect of cardiotomy suction, we developed an automatic controlled cardiotomy suction system by which the aspiration of air along with suction of blood was prevented. We introduced this system clinically during membrane oxygenator perfusions in CABG operations of various duration (6), and found that controlled suction indeed reduced platelet activation. This was indicated by the significantly lower beta-thromboglobulin plasma concentration, which occured during perfusions of approximately 2 hours. However, hemolysis was hardly decreased



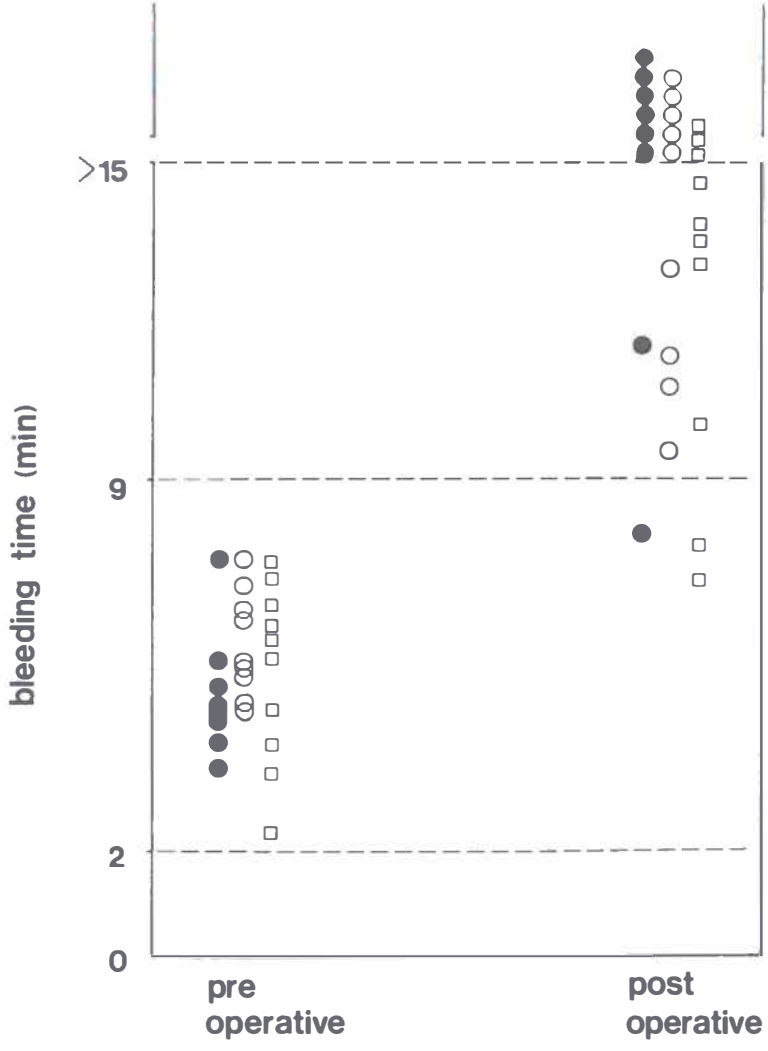
Legend to figure 1:
Mean values and standard errors of the mean of platelet number, platelet function (ADP induced platelet aggregation) and beta-thromboglobulin plasma concentration (BTG), before, during and immediately after perfusion. Platelet function is expressed as a percentage of preperfusion values.
● = bubble oxygenator with uncontrolled suction
○ = bubble oxygenator with controlled suction
□ = membrane oxygenerator with uncontrolled suction
* = $p < 0.05$ (Student's T test).

in these perfusions of 2 hours. The platelet preserving capacity of controlled suction became even more apparent in membrane oxygenator perfusions of longer duration, i.e. of approximately 3 hours. As a result, blood loss measured up to 18 hours after the end of perfusion was significantly reduced when compared to blood loss after perfusions with uncontrolled suction. Because this substantial improvement by controlled suction was obtained during perfusions with a better hemocompatible membrane oxygenator system, it was of interest if the hemocompatible inferior bubble oxygenator system could also be improved by controlled suction. We therefore performed this present study and used controlled suction in CABG operations with bubble oxygenator perfusions of the same duration of approximately 3 hours.
We excluded the arterial line filter, which is not mandatory in a membrane oxygenator system, from the bubble oxygenator system during perfusion because this filter might partly increase platelet and erythrocyte damage (8,22). Therefore it might have made comparisons between the three groups inaccurate.



Legend to figure 2:
Mean values and standard errors of the mean of plasma hemoglobin, before, during and immediately after perfusion.
● = bubble oxygenator with uncontrolled suction
○ = bubble oxygenator with controlled suction
□ = membrane oxygenator with uncontrolled suction
* = $p < 0.05$ (Student's T test).

We found that controlled suction during bubble oxygenator perfusions did not reduce platelet damage significantly, nor did it improve postoperative hemostasis but it did reduce hemolysis significantly. ADP-induced platelet aggregation decreased almost progressively in the bubble oxygenator system as perfusion continued, caused by the platelet damaging effect of the conti-



Legend to figure 3:
Pre- and postoperative bleeding times related to the type of oxygenator and method of cardiotomy suction. Normal bleeding time is 2-9 minutes. Differences between the three groups are not significant (Wilcoxon's test, $p > 0.05$)
● = bubble oxygenator with uncontrolled suction
○ = bubble oxygenator with controlled suction
□ = membrane oxygenator with uncontrolled suction

nuous gas-bubble stream through the blood (14,23,24). In contrast during the membrane oxygenator perfusions platelet damage was significantly less, as indicated by the lower level of platelet activation (lower BTG plasma concentration), a better preserved ADP-induced platelet aggregation and a significantly higher platelet number.
After the end of aortic crossclamping, when cardiotomy suction is in particular required, platelet number and ADP-induced platelet aggregation decreased significantly in both bubble oxygenator groups, whereas they increased in the membrane oxygenator group. Consequently platelets were significantly better preserved in the membrane oxygenator group. On the other hand this indicates that there is probably a potentiating effect on platelet damage induced by the bubble oxygenator system, but not by the membrane oxygenator system. This means that the platelet preserving capacity of controlled suction was completely lost by the damaging effect of the bubble oxygenator system. This was clearly shown in the BTG plasma concentrations, a sensitive indicator of platelet activation, which were very high in both bubble oxygenator groups but not significantly different among both groups. On the other hand these measurements indicated that when platelets are well preserved during the membrane oxygenator perfusion, the platelet damaging effect of uncontrolled suction was relatively small. This is demonstrated by only a small increase in BTG plasma concentration after release of the aortic crossclamp.
In all patients bleeding times increased significantly postoperatively, but did not differ significantly between the three groups (13,15). Probably therefore the mean postoperative blood loss and volume of donor blood transfusions, measured up to 18 hours after the end of perfusion was the same in all three groups. However, the significant reduction in hemolysis in the bubble oxygenator group with controlled suction as compared to uncontrolled suction, demonstrated the valuable effect of controlled suction in reducing erythrocyte damage during the bubble oxygenator perfusion.
In conclusion, this study indicates that in CABG operations of approximately 3 hours, during which large volumes of cardiotomy suction occur, the hemocompatibility of the bubble oxygenator can only be improved partly by using controlled cardiotomy suction as indicated by a reduction in hemolysis. However, its platelet preserving capacity was completely lost by the platelet damaging effect of the bubble oxygenator. The platelet preserving capacity of controlled suction can be maintained if it is combined with a membrane oxygenator perfusion, as was demonstrated elsewhere (6,7).

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CHAPTER 7

SUMMARY

SUMMARY

This thesis evaluates the platelet damage by "uncontrolled" cardiotomy suction, which implies the aspiration of air along with suction of blood, during clinical cardiopulmonary bypass (CPB) in open heart surgery. This damaging effect of uncontrolled cardiotomy suction can be eliminated when the air aspiration is prevented, so called "controlled" cardiotomy suction. This system consists of a special sucker with two electrodes mounted on the tip of the sucker and that are connected to an electronic regulating device. These two electrodes are supplied with a high frequency voltage (30 kHz). The current between both electrodes is directly proportional to the blood level in between them and it is the signal for the regulating device, which regulates the r.p.m. of the roller pump. This device keeps the blood in the operation area at a constant negligibly low level and it prevents the aspiration of air. The device can be switched immediately to "manual" if a completely dry operation area is required. In particular the preserving effect of controlled cardiotomy suction on platelets and postoperative hemostasis in relation to the different components of the extracorporeal circuit like the type of oxygenator, arterial line filter and total amount of cardiotomy suction, is the main subject of this thesis.

Chapter 1 is a general introduction to this thesis, in order to emphasize the central role of the platelet in the maintainance of the vessel wall integrity and postoperative hemostasis. In Chapter 2 we studied the total amount of blood return to the oxygenator in patients undergoing CPB for various types of cardiac operations and varying perfusion times, in order to define a group of patients in which the effects of cardiotomy suction on platelets and postoperative hemostasis could be studied in a standardized way. Patients undergoing a coronary artery bypass grafting (CABG) operation with a perfusion time of approximately 3 hours had a rather large and constant volume of cardiotomy blood return and were the patient group of choice. Other types of operation or other perfusion times were less appropiate, because of larger variations in the total amount of blood return, larger variation in age and lower incidence when compared to these CABG operations.
In Chapter 3 we determined in this defined group of patients whether the hematological advantage of the membrane oxygenator over the bubble oxygenator is indeed lost by the platelet damaging effect of uncontrolled cardiotomy suction. We found that the membrane oxygenator still caused significantly less platelet and erythrocyte damage than the bubble oxygenator, despite the damaging effects of uncontrolled cardiotomy suction. However, the differences between the BO and MO in platelet damage as well as in postoperative blood loss and blood transfusions in this study during long perfusions of approximately 3 hours, were less pronounced than the differences between both oxygenators found in a previous study by Van den Dungen

(1982) which was focussed on shorter perfusions of approximately 2 hours. This impairement of the hematological superiority of the MO over the BO is most likely explained by the larger amounts of cardiotomy suction which we had measured in these longer perfusions.

In Chapter 4 we evaluated to what extent the arterial line filter in the BO system was responsible for the difference in hemocompatibility between the BO and the MO system because an arterial line filter is not used in the MO system. We found that the arterial line filter impaired the hemocompatibility of the BO system only to a small extent, and that it is responsible only in a small part for the differences between both oxygenator systems.

In Chapter 5 we compared the results of the effect of controlled cardiotomy suction with the results of uncontrolled cardiotomy suction on platelets during MO perfusions with varying duration. We found that controlled cardiotomy suction significantly reduced platelet activation and postoperative blood loss, particulary when large volumes of blood were aspirated. This observation substantiated the conclusion made in Chapter 2, that uncontrolled cardiotomy suction obscures the hematological superiority of the MO over the BO.

In Chapter 6 we determined whether controlled suction could also improve the hemocompatibility of a BO system. However, we found that the platelet preserving capacity of controlled cardiotomy suction was completely lost by the platelet damaging effect of the BO, although the reduction in hemolysis was well maintained.

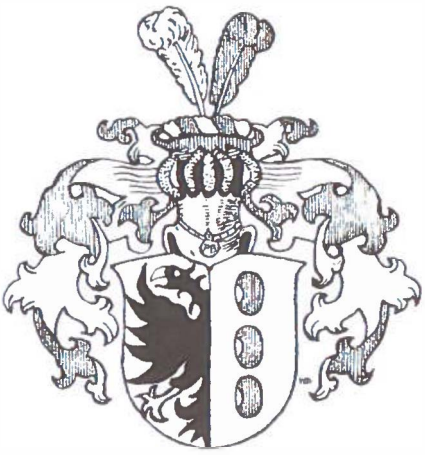
CHAPTER 8

SAMENVATTING

SAMENVATTING

Een van de belangrijkste nadelige gevolgen van het gebruik van de hartlongmachine in de hartchirurgie is de bloedbeschadiging. Deze bloedbeschadiging kan in ongeveer 4 % van de gevallen na de operatie leiden tot een ernstig verhoogde bloedingsneiging met veel bloedverlies. Talrijke onderzoekers toonden aan, dat een beschadiging van de bloedplaatjes, die een centrale rol spelen in de bloedstelping, een van de belangrijkste oorzaken is van deze verhoogde bloedingsneiging.
Uit dierexperimenteel en klinisch onderzoek bleek de beschadiging van bloedplaatjes voornamelijk veroorzaakt te worden door de kunstlong van de hartlongmachine. Van de tegenwoordig gebruikte types kunstlongen, de bubble long en de recentelijk geïntroduceerde membraan long, leidt de laatstgenoemde tot veel minder beschadiging van de bloedplaatjes en dientengevolge ook tot een geringere bloedingsneiging na de operatie. Derhalve neigt men er tegenwoordig steeds meer toe de membraan long te gebruiken tijdens hartoperaties. Echter dit voordeel van de membraan long kon niet door alle onderzoekers klinisch worden aangetoond. Om meer inzicht in deze materie te verkrijgen verrichtten De Jong en Ten Duis hematologische studies tijdens gestandaardiseerde hartoperaties bij honden. Hieruit bleek dat het voordeel van de membraan long in belangrijke mate teniet kon worden gedaan door de beschadigende werking van het wegzuigen van bloed uit het operatiegebied. Deze beschadigende werking van bloedzuigen wordt veroorzaakt door het gelijktijdig meezuigen van lucht, "slobberen", waardoor wervelingen in het bloed ontstaan die grote schuifspanningen en daardoor beschadigingen veroorzaken aan de bloedcellen: we noemen dit ongecontroleerd bloedzuigen. Om dit nadelige effect van het ongecontroleerd zuigen van bloed te voorkomen, werd een systeem ontworpen waarmee het aanzuigen van lucht kon worden voorkomen: we noemen dit gecontroleerd bloedzuigen. In de dierexperimentele studies van De Jong werd dit zuigsysteem getest en het bleek, dat dit zuigsysteem inderdaad beschadigingen van de bloedplaatjes kon voorkomen en dientengevolge de bloedingsneiging na de operatie kon verminderen. Door gebruik te maken van dit gecontroleerd bloedzuigsysteem kon in het dierexperiment het voordeel van de membraan long behouden blijven.
Wat de effecten van gecontroleerd bloedzuigen zijn bij patienten die een hartoperatie ondergaan blijkt uit de in dit proefschrift beschreven onderzoeken. Deze onderzoeken zijn gericht op de effecten van het bloedzuigen op bloedplaatjes tijdens de operatie, en op de bloedingsneiging na de operatie. De effecten van bloedzuigen zijn bestudeerd in relatie tot de bloedplaatjes beschadigende effecten van enkele andere componenten van de hartlongmachine, zoals het type kunstlong en het filter in de bloedstroombaan van de hartlongmachine maar eveneens in relatie tot de totale hoeveelheid gezogen bloed en de operatieduur.

Hoofdstuk 1 is een algemene inleiding van dit proefschrift en beschrijft in het kort de centrale rol van het bloedplaatje binnen de bloedstelping. In hoofdstuk 2 hebben wij 4 verschillende types operaties van verschillende tijdsduur bestudeerd, en maten de totale hoeveelheid bloed die tijdens deze operaties wordt weggezogen uit het operatieterrein, teneinde een groep patienten te vinden waarbij het effect van bloedzuigen op de bloedplaatjes op een gestandaardiseerde wijze bestudeerd kon worden. Wij kozen voor de patienten die een kransvat-omleidings-operatie moesten ondergaan en waarvan de duur van de operatie ongeveer 3 uur zou bedragen, aangezien juist tijdens deze operaties een tamelijk grote en constante hoeveelheid bloed gezogen werd. Andere groepen patienten waren minder geschikt vanwege de grote variaties in de totale hoeveelheid bloed die gezogen werd, de grote variaties in leeftijd van de patienten, en de lagere frequentie van deze operatietypes. In hoofdstuk 3 hebben wij de bloedplaatjes beschadiging tengevolge van het ongecontroleerde bloed zuigen in relatie tot het gebruikte type kunstlong onderzocht. We gingen bij de geselecteerde groep patienten na of ongecontroleerd bloedzuigen inderdaad het voordelige effect van de membraan long teniet kon doen. Dit bleek inderdaad - gedeeltelijk - het geval te zijn. In hoofdstuk 4 hebben we de beschadiging van bloedplaatjes onderzocht, die ontstaat ten gevolge van de aanwezigheid van een filter dat alleen gebruikt wordt in de bloedstroombaan van een bubble long. Dit filter bleek slechts voor een zeer gering deel bij te dragen aan de verschillen in bloedplaatjes beschadiging tussen beide kunstlongen. In hoofdstuk 5 hebben wij de bloedplaatjes beschadiging in relatie tot verschillende hoeveelheden gezogen bloed en de operatieduur bestudeerd, waarbij de effecten van gecontroleerd en ongecontroleerd bloedzuigen met elkaar werden vergeleken. Deze onderzoeken zijn verricht tijdens hartoperaties uitgevoerd met een membraan long. Het gecontroleerde bloedzuigen bleek inderdaad de bloedplaatjes beschadiging en de bloedingsneiging na de operatie significant te kunnen verminderen. Vooral naarmate de operaties langer duurden en er meer bloed werd gezogen, bleek het voordelige effect van gecontroleerd bloedzuigen steeds duidelijker naar voren te komen. Deze bevindingen bevestigden de conclusie die in hoofdstuk 2 reeds was gemaakt, dat ongecontroleerd bloedzuigen de voordelen van de membraan long nadelig kan beïnvloeden, in het bijzonder bij langdurige operaties. In hoofdstuk 6 hebben wij de bloedplaatjes beschadiging tijdens en de bloedingsneiging na de operatie tengevolge van het ongecontroleerde bloedzuigen bij het gebruik van een bubble long vergeleken met de resultaten van gecontroleerd bloedzuigen. Het bleek dat de voordelige effecten van gecontroleerd bloedzuigen volledig verloren gingen door de beschadigende werking van de bubble long.



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